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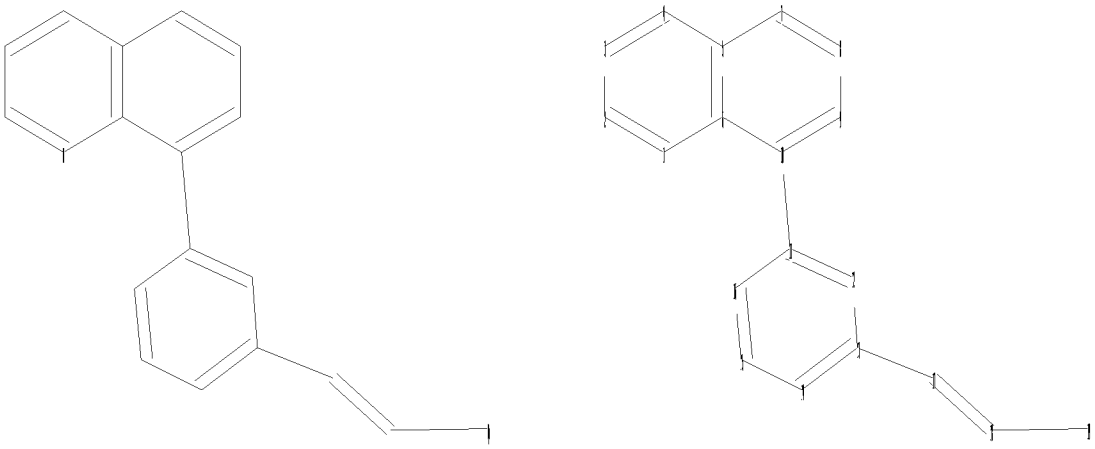
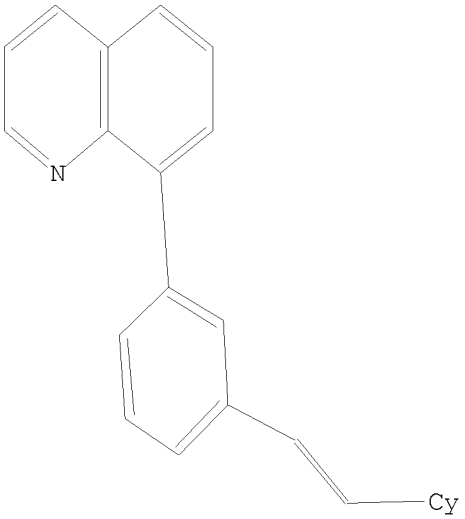


chain nodes :
17 18 19
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
chain bonds :
10-11 13-17 17-18 18-19
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14
14-15 15-16
exact/norm bonds :
18-19
exact bonds :
10-11 13-17 17-18
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14
14-15 15-16

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:Atom

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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FULL SEARCH INITIATED 11:46:52 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      388 TO ITERATE

100.0% PROCESSED      388 ITERATIONS                                93 ANSWERS
SEARCH TIME: 00.00.01

L2            93 SEA SSS FUL L1

=> d l2 1-10

L2   ANSWER 1 OF 93  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   1027957-73-8  REGISTRY
ED   Entered STN:  13 Jun 2008
CN   6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(3-methyl-
     1,2,4-oxadiazol-5-yl)-1-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-  (CA
     INDEX NAME)
FS   STEREOSEARCH
MF   C31 H26 N4 O3 S
SR   Other Sources
       Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.
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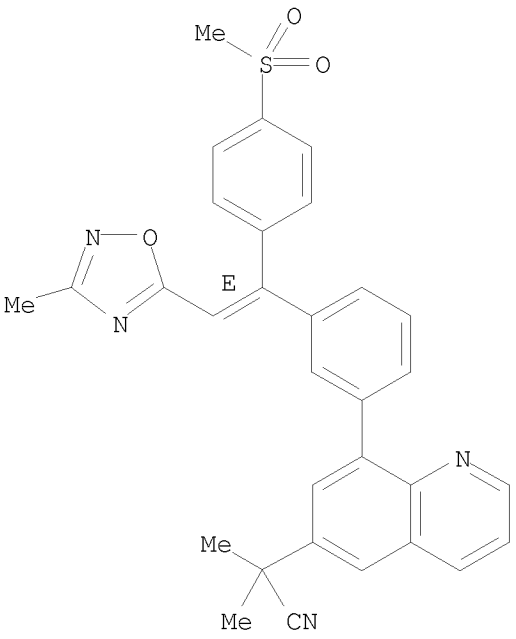
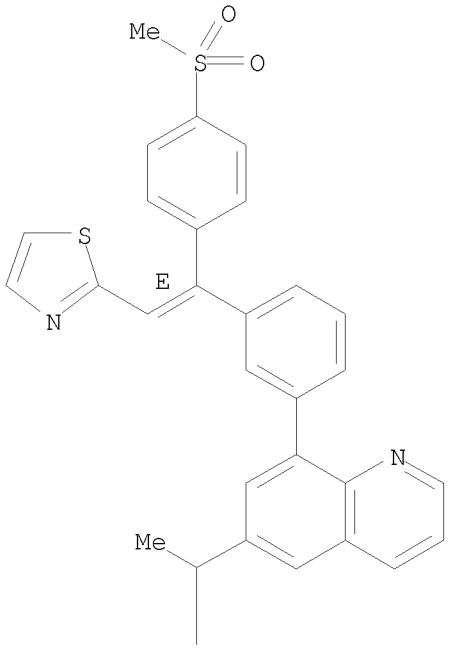


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

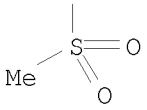
L2 ANSWER 2 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1027585-23-4 REGISTRY
ED Entered STN: 12 Jun 2008
CN Quinoline, 6-[1-(methylsulfonyl)ethyl]-8-[3-[(1E)-1-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H26 N2 O4 S3
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

PAGE 1-A



PAGE 2-A

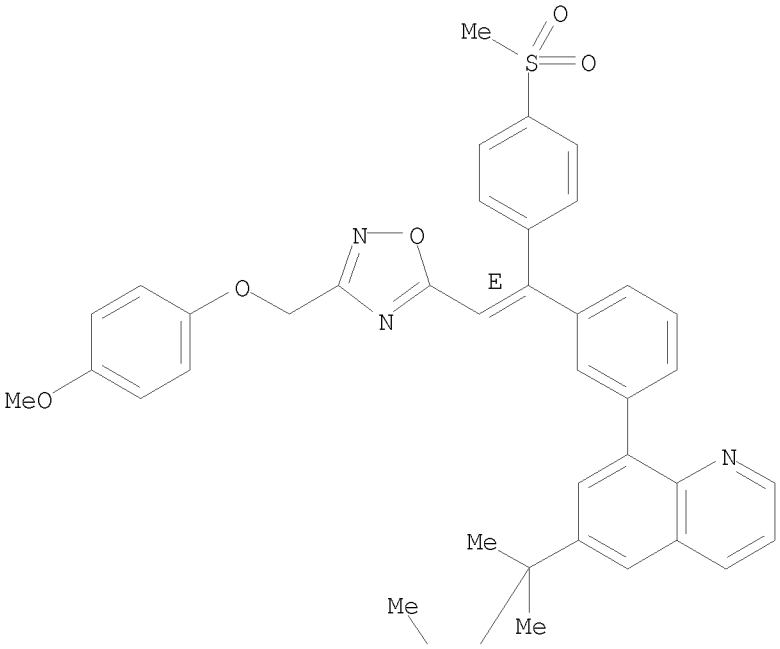


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 3 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1027513-98-9 REGISTRY
ED Entered STN: 12 Jun 2008
CN Quinoline, 8-[3-[(1E)-2-[3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-1-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C38 H35 N3 O7 S2
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

PAGE 1-A



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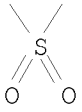
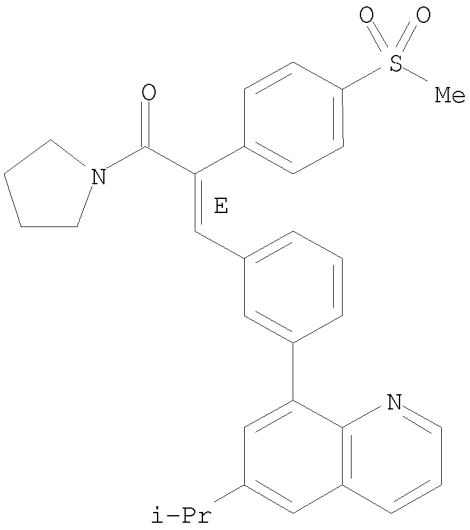


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 4 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1027499-88-2 REGISTRY
ED Entered STN: 12 Jun 2008
CN 2-Propen-1-one, 3-[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-, (2E)- (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H32 N2 O3 S
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.



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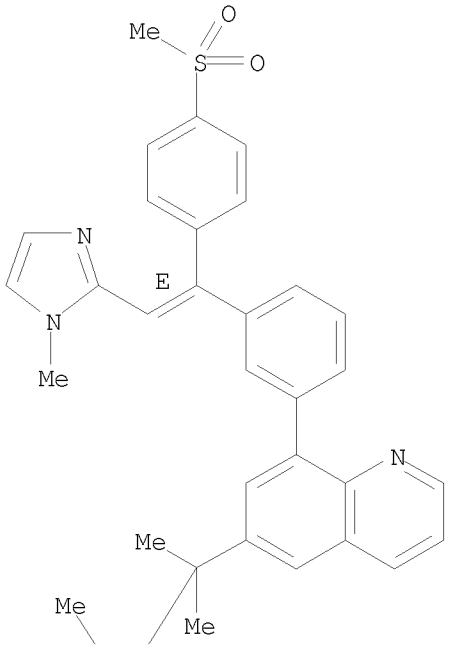
L2 ANSWER 5 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1027307-49-8 REGISTRY
ED Entered STN: 11 Jun 2008
CN Quinoline, 8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H31 N3 O4 S2
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

PAGE 1-A



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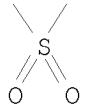
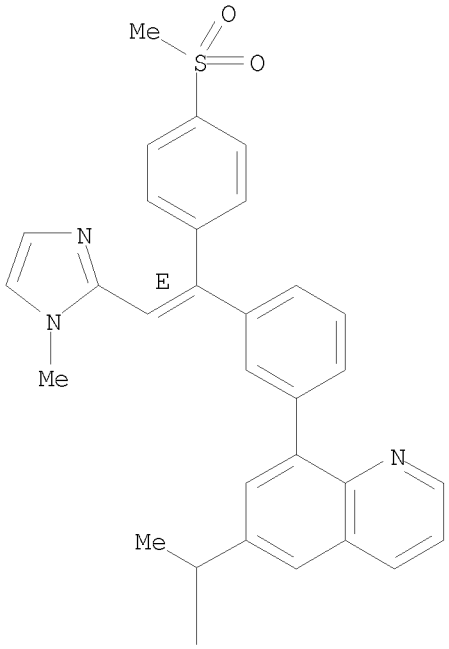


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 6 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1027204-70-1 REGISTRY
ED Entered STN: 11 Jun 2008
CN Quinoline, 8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-(methylsulfonyl)ethyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H29 N3 O4 S2
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

PAGE 1-A



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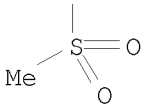
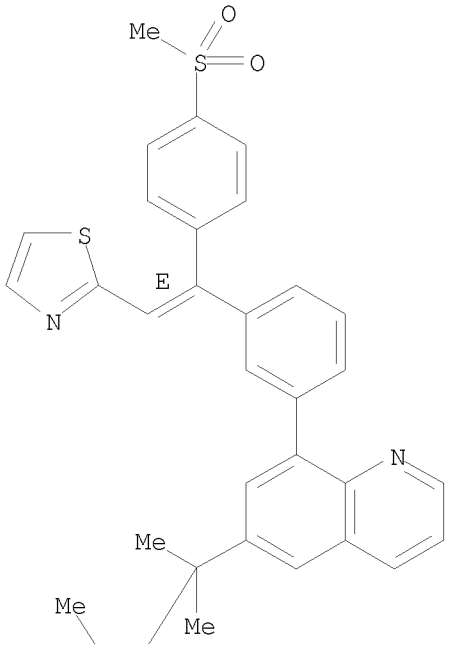


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 7 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1027196-45-7 REGISTRY
ED Entered STN: 11 Jun 2008
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-1-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H28 N2 O4 S3
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

PAGE 1-A



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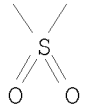
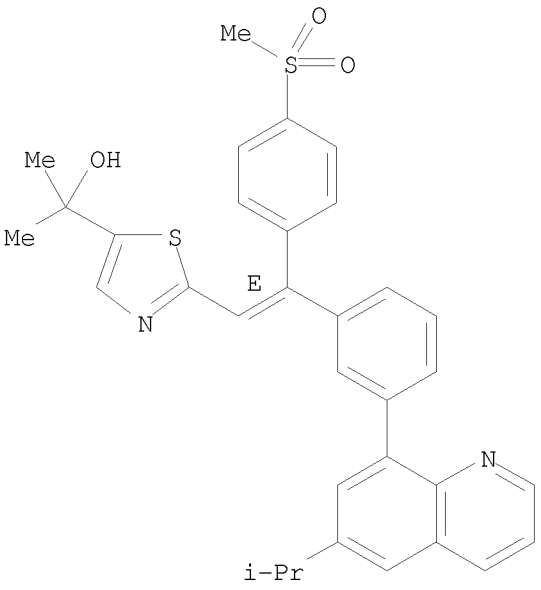


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 8 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1026959-72-7 REGISTRY
ED Entered STN: 10 Jun 2008
CN 5-Thiazolemethanol, α,α-dimethyl-2-[(1E)-2-[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H32 N2 O3 S2
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.



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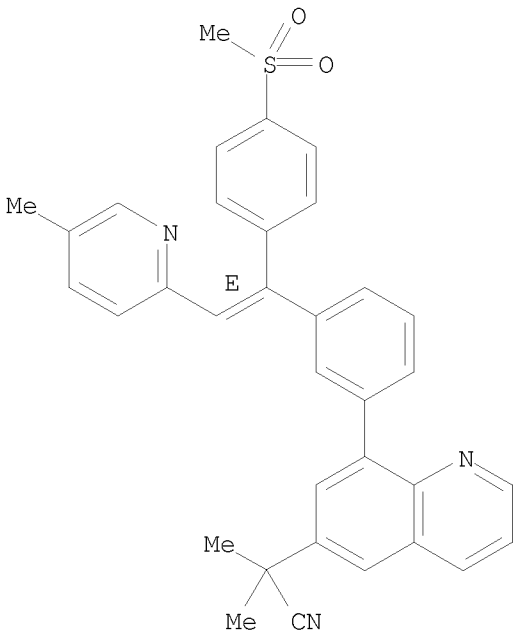
L2 ANSWER 9 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1026883-38-4 REGISTRY
ED Entered STN: 10 Jun 2008
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H29 N3 O2 S
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

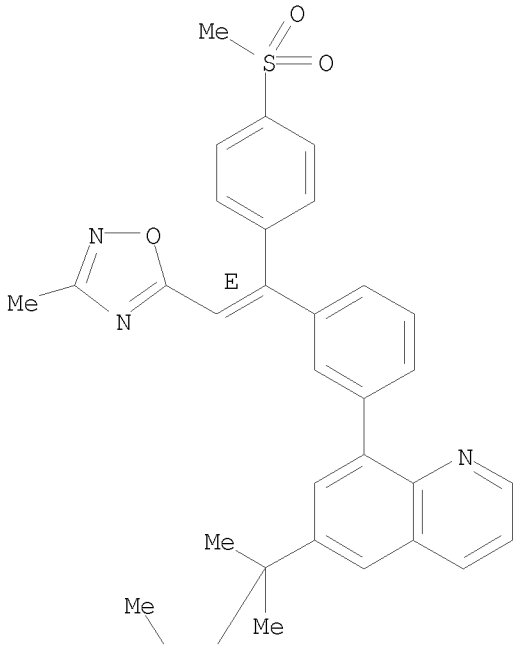


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 10 OF 93 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1026793-27-0 REGISTRY
ED Entered STN: 09 Jun 2008
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-1-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H29 N3 O5 S2
SR Other Sources
Database: ChemSpider (ChemZoo, Inc.)

Double bond geometry as shown.

PAGE 1-A



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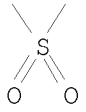

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

=>
=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	213.08	213.29

FILE 'CAPLUS' ENTERED AT 12:06:29 ON 18 JUN 2008

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FILE COVERS 1907 - 18 Jun 2008 VOL 148 ISS 25
FILE LAST UPDATED: 17 Jun 2008 (20080617/ED)

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=> s l2
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116942 ?HYDRAZIN?
L4 2 L3 AND ?HYDRAZIN?

=> d l4 1-2 ibib abs hitstr

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:267275 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 140:303679
TITLE: Removal of an aldehyde impurity from a substituted 8-arylquinoline by treatment with a reactive polystyrene sulfonylhydrazine resin
INVENTOR(S): Biba, Mirlinda; Collins, Paul Compton; Welch, Christopher Joseph; Conlon, David A.; Drahus, Antoinette
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004026794	A2	20040401	WO 2003-US28716		20030912
WO 2004026794	A3	20040617			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2003272347	A1	20040408	AU 2003-272347		20030912
EP 1545526	A2	20050629	EP 2003-754525		20030912
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US 20070054941	A1	20070308	US 2005-526782		20050304
PRIORITY APPLN. INFO.:			US 2002-411245P	P	20020917
			WO 2003-US28716	W	20030912

OTHER SOURCE(S): MARPAT 140:303679
GI

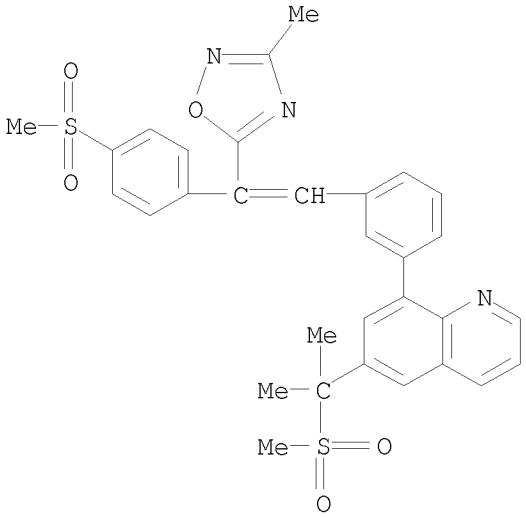
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A purification method of a substituted 8-arylquinoline (I) utilizes contacting the I with a DMF-swelled polystyrene-based sulfonylhydrazine reactive resin to remove the 8-(3-formylphenyl)quinoline impurity (II).

IT 676323-87-8P
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(removal of an aldehyde impurity from a substituted 8-arylquinoline by treatment with a reactive polystyrene sulfonylhydrazine resin)

RN 676323-87-8 CAPLUS

CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)



L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:22685 CAPLUS <<LOGINID::20080618>>

DOCUMENT NUMBER: 138:73184

TITLE: Preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors

INVENTOR(S): Dube, Daniel; Girard, Yves; MacDonald, Dwight; Mastracchio, Anthony; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis

PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.

SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2003002118		A1	20030109	WO 2002-CA953	20020626
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2450686		A1	20030109	CA 2002-2450686	20020626
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AU 2002344885		B2	20060629		
EP 1404330		A1	20040407	EP 2002-742600	20020626
EP 1404330		B1	20050601		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005501822		T	20050120	JP 2003-508357	20020626
AT 296630		T	20050615	AT 2002-742600	20020626
ES 2242036		T3	20051101	ES 2002-742600	20020626
US 20040162314		A1	20040819	US 2003-478791	20031125
US 6919353		B2	20050719		
PRIORITY APPLN. INFO.:				US 2001-301220P	P 20010627
				US 2001-303472P	P 20010706
				WO 2002-CA953	W 20020626

OTHER SOURCE(S): MARPAT 138:73184
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

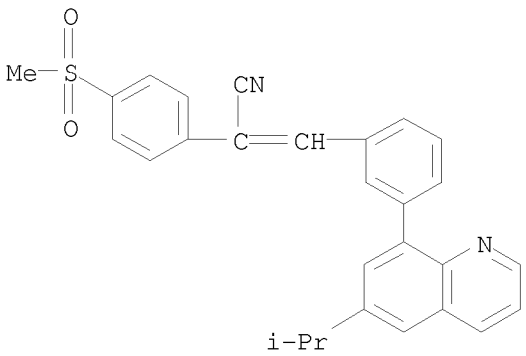
AB 8-Arylquinolines (shown as I; variables defined below; e.g. both enantiomers of 4-hydroxy-1-[3-[6-(1-methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)-4-methylpentan-3-one) wherein the aryl group at the 8-position contains a meta two atom bridge to an optionally substituted Ph or pyridyl group, are PDE4 inhibitors useful to treat asthma, chronic bronchitis, chronic obstructive pulmonary disease, arthritis, respiratory distress syndrome, allergic rhinitis, neurogenic inflammation, pain, rheumatoid arthritis, and other diseases. R1-R7 and Ar are as in claim 1. For I: Ar is Ph, pyridinone, pyridyl, or pyridyl N-oxide, optionally substituted with 1-5 independent -C1-6-alkyl, -OH, -CN, halogen, -CF3, -(C0-6-alkyl)-SOn-(C1-6-alkyl), -(C0-6-alkyl)-SOn-NH-(C1-6-alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N, wherein the 5-membered-ring is optionally substituted. R1 is H, halogen; or a -C1-6-alkyl, -cycloC3-6alkyl, -C1-6-alkenyl, -C0-4alkyl-C(O)-C0-4alkyl, -C1-6-alkoxy, aryl, heteroaryl, -CN, -heterocycloC3-6-alkyl, -amino, -C1-6-alkylamino, -(C1-6-alkyl)(C1-6-alkyl)amino, -C1-6-alkyl(oxy)C1-6-alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SOnNH(aryl), -SOnNH(heteroaryl), -SOnNH(C1-6-alkyl), -C(O)N(C0-6alkyl)(C0-6-alkyl), -NH-SOn-(C1-6-alkyl), -carbamoyl, -(C1-6-alkyl)-O-C(CN)dialkylamino, or -(C0-6-alkyl)-SOn-(C1-6-alkyl) group, wherein any of the groups is optionally substituted with = 1-5 substituents. R2, R3, R6, and R7 = H, halogen, hydroxy, -C1-6-alkyl, or -C1-6-alkoxy, wherein the alkyl and alkoxy are optionally substituted independently with 1-3 halogen or OH; R4 is H, halogen, -CN, Ph, oxadiazolyl, or -C(O)-O-C0-6alkyl, wherein the alkyl and latter three possibilities are optionally substituted. R5 is H, hydroxy, -CN; or a -C1-6-alkyl, -C(O)C1-6alkyl, -C(O)aryl, -C(O)pyridyl, -C(O)-O-C0-6-alkyl, -C(O)-C3-7-cycloalkyl, -C1-6-alkyl-C3-7cycloalkyl, -C1-6-alkyl(C3-7-

cycloalkyl)2, -C1-6-alkylaryl, -C(O)-N(C0-6alkyl)2, -SOnaryl, -SOn-C1-6-alkyl, -SOn-C3-7-cycloalkyl, -SOn-N(C0-6-alkyl)2, -P(O)(C1-6-alkyl)2, -P(O)(C1-6-alkoxy)2, Ph, pyridyl, -SOnimidazolyl, -SOnthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted; or R5 and R6 form :O; or R6 and R3 form -CH2- or -O-; and n is 0-2. Although the methods of preparation are not claimed, >100 example prepns. are included. The IC50 values for PDE4 inhibition of Examples 1-113 generally are 0.02-26 μM as measured using LPS and FMLP-induced TNF-α and LTB4 assays in human whole blood. I were tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs;. Administration of I (0.001-10 mg/kg i.p. or p.o.), up to three times during the 48 h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with I. Compds. which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format; IC50 values of I generally ranged 0.1-25 nM.

IT 481680-70-0P, 3-[3-(6-Isopropylquinolin-8-yl)phenyl]-2-[4-(methylsulfonyl)phenyl]prop-2-enenitrile 481680-74-4P, 3-[3-[6-(Cyanodimethylmethyl)quinolin-8-yl]phenyl]-N-isopropyl-2-(4-methanesulfonylphenyl)acrylamide 481680-96-0P, 3-[3-[6-(1-Methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)acrylic acid 481680-97-1P, 3-[3-[6-(1-Methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)acrylic acid methyl ester 481681-05-4P, 8-[4-Fluoro-3-[2-(4-methanesulfonylphenyl)vinyl]phenyl]-6-isopropylquinoline 481681-15-6P, 3-[3-(6-Isopropylquinolin-8-yl)phenyl]-2-pyridin-4-ylacrylonitrile
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors)

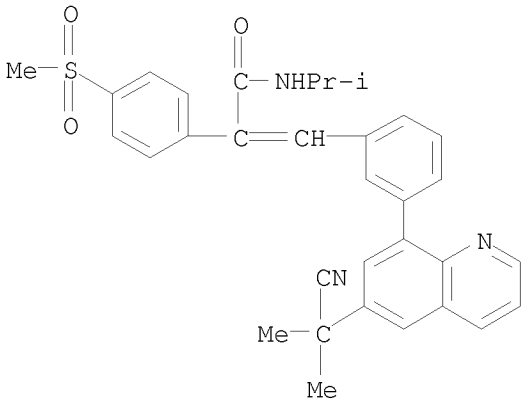
RN 481680-70-0 CAPLUS

CN Benzeneacetonitrile, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)- (CA INDEX NAME)

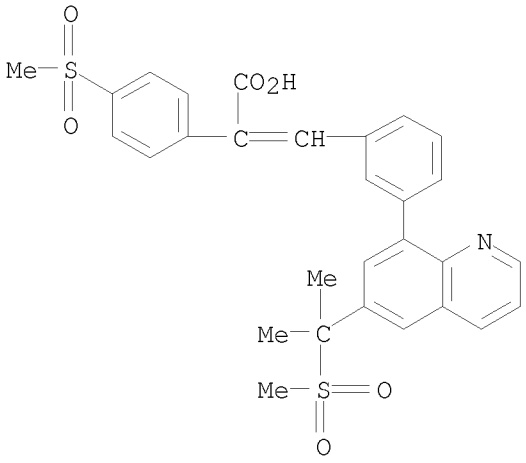


RN 481680-74-4 CAPLUS

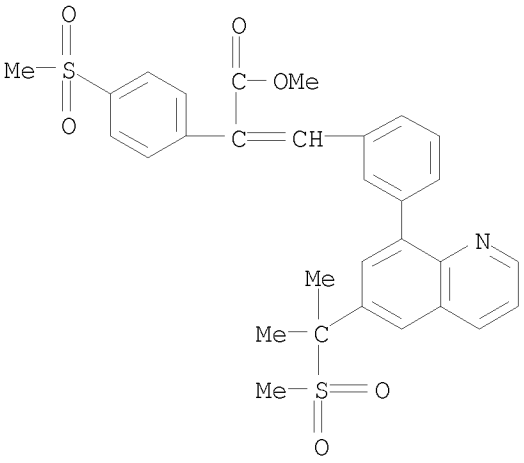
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)- (CA INDEX NAME)



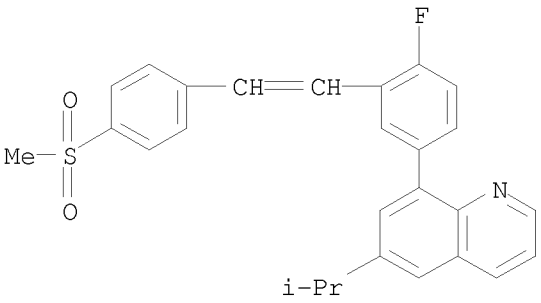
RN 481680-96-0 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)- (CA INDEX NAME)



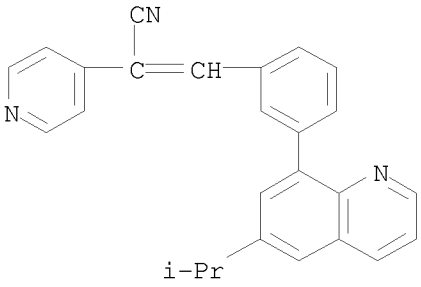
RN 481680-97-1 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, methyl ester (CA INDEX NAME)



RN 481681-05-4 CAPLUS
CN Quinoline, 8-[4-fluoro-3-[2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)



RN 481681-15-6 CAPLUS
CN 4-Pyridineacetonitrile, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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        164605 ?POLYSTYREN?
L5           1 L3 AND ?POLYSTYREN?

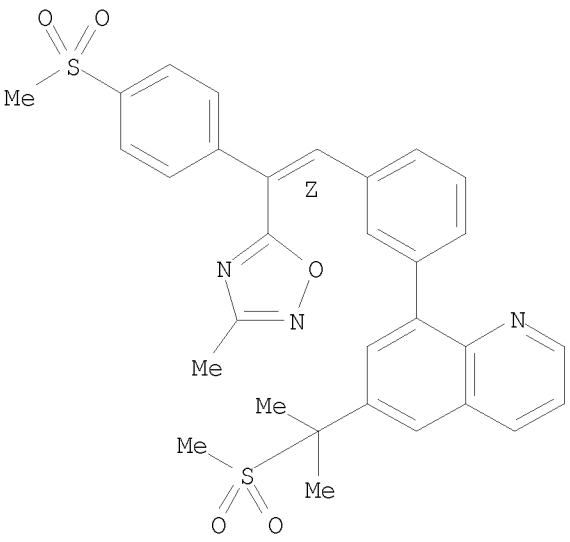
=> s l3 and ?resin?
        854531 ?RESIN?
L6           1 L3 AND ?RESIN?

=> s l3 and ?aldehyd?
        623133 ?ALDEHYD?
L7           7 L3 AND ?ALDEHYD?

=> d l7 1-7 ibib abs hitstr

L7   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2005:1288278  CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER:          144:173096
TITLE:                    Process Development and Large-Scale Synthesis of a
                          PDE4 Inhibitor
AUTHOR(S):                Conlon, David A.; Drahus-Paone, Antoinette; Ho,
                          Guo-Jie; Pipik, Brenda; Helmy, Roy; McNamara, James
                          M.; Shi, Yao-Jun; Williams, J. Michael; Macdonald,
                          Dwight; Deschenes, Denis; Gallant, Michel;
                          Mastracchio, Anthony; Roy, Bruno; Scheigetz, John
CORPORATE SOURCE:         Department of Process Research and Department of
                          Analytical Research, Merck Research Laboratories,
                          Rahway, NJ, 07065-0900, USA
SOURCE:                   Organic Process Research & Development (2006), 10(1),
                          36-45
                          CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
OTHER SOURCE(S):          CASREACT 144:173096
AB   An efficient, scalable synthesis of the PDE4 inhibitor,
     6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-{(E)-2-(3-methyl-1,2,4-oxadiazol-
     5-yl)-2-[4-(methylsulfonyl)phenyl]vinyl}phenyl)quinoline benzenesulfonate
     (1) is described.  The synthesis is highly convergent, generating the
     penultimate 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-(3-methyl-
     1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]vinyl]phenyl]quinoline
     by coupling 3-[6-[1-Methyl-1-(methylsulfonyl)ethyl]quinolin-8-yl]
     benzaldehyde (2) and 3-Methyl-5-[4-(methylsulfonyl)benzyl]-1,2,4-
     oxadiazole (3) via Knoevenagel reaction.  The process consists of a total
     of nine chemical steps, five of which comprise the sequence to prepare 2 via
     Skraup reaction, bromination, sulfone formation, methylation and
     Suzuki-Miyaura cross-coupling, and a two-step sequence for the synthesis
     of 3 that includes the methylamidoxime and oxadiazole steps.  The final
     two steps are Knoevenagel coupling and salt formation.  The process
     produced the drug candidate 1 in 46% overall yield from
     2-bromo-4-methylaniline on multikilogram scale.
IT   346629-31-0P
     RL: BYP (Byproduct); PREP (Preparation)
        (process development and reaction sequence for large-scale synthesis of
        oxadiazolylmethylsulfonyl phenylquinoline PDE4 inhibitor)
RN   346629-31-0  CAPLUS
CN   Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1Z)-2-(3-methyl-
     1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-  (CA
     INDEX NAME)

Double bond geometry as shown.
```



IT 346630-09-9P, 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]vinyl]phenyl]quinoline benzenesulfonate
RL: IMF (Industrial manufacture); PREP (Preparation)
(process development and reaction sequence for large-scale synthesis of oxadiazolylmethylsulfonyl phenylquinoline PDE4 inhibitor)

RN 346630-09-9 CAPLUS

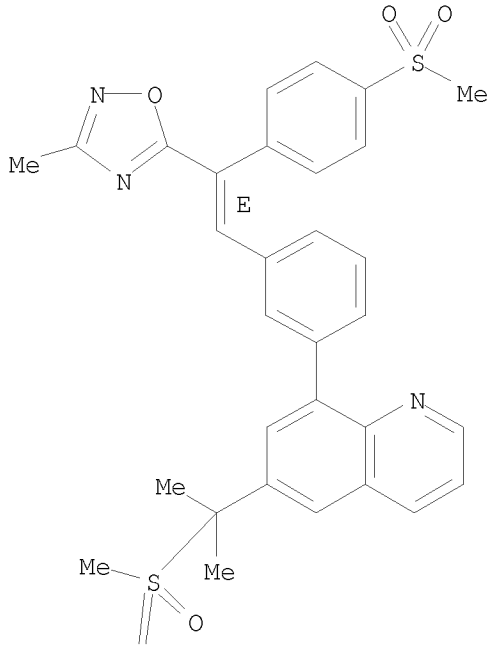
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-, benzenesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 346629-30-9
CMF C31 H29 N3 O5 S2

Double bond geometry as shown.

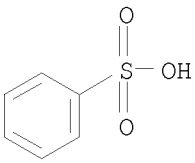
PAGE 1-A



PAGE 2-A

CM 2

CRN 98-11-3
CMF C6 H6 O3 S

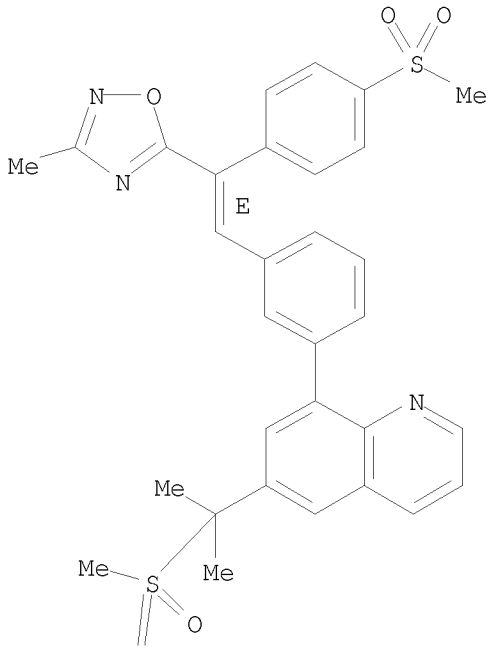


IT 346629-30-9P, 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]vinyl]phenyl]quinoline
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(process development and reaction sequence for large-scale synthesis of oxadiazolylmethylsulfonyl phenylquinoline PDE4 inhibitor)
RN 346629-30-9 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-

1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

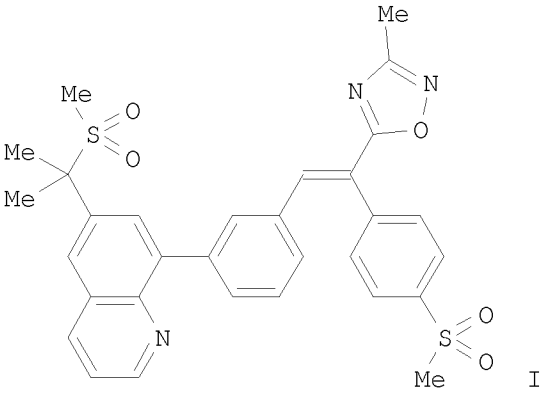


PAGE 2-A

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1144493 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 144:51429
TITLE: Discovery of a substituted 8-arylquinoline series of PDE4 inhibitors: Structure-activity relationship, optimization, and identification of a highly potent, well tolerated, PDE4 inhibitor
AUTHOR(S): Macdonald, Dwight; Mastracchio, Anthony; Perrier, Helene; Dube, Daniel; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis; Roy, Bruno; Scheigetz, John; Bateman, Kevin; Li, Chun; Trimble, Laird A.; Day, Stephen; Chauret, Nathalie; Nicoll-Griffith, Deborah A.; Silva, Jose M.; Huang, Zheng; Laliberte, France; Liu, Susana; Ethier, Diane; Pon, Doug; Muise, Eric; Boulet, Louise; Chan, Chi Chung; Styhler, Angela; Charleson, Stella; Mancini, Joseph; Masson, Paul; Claveau, David; Nicholson, Donald; Turner,

Mervyn; Young, Robert N.; Girard, Yves
CORPORATE SOURCE: Merck Frosst Centre for Therapeutic Research, Pointe Claire-Dorval, QC, H9R 4P8, Can.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(23), 5241-5246
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:51429
GI

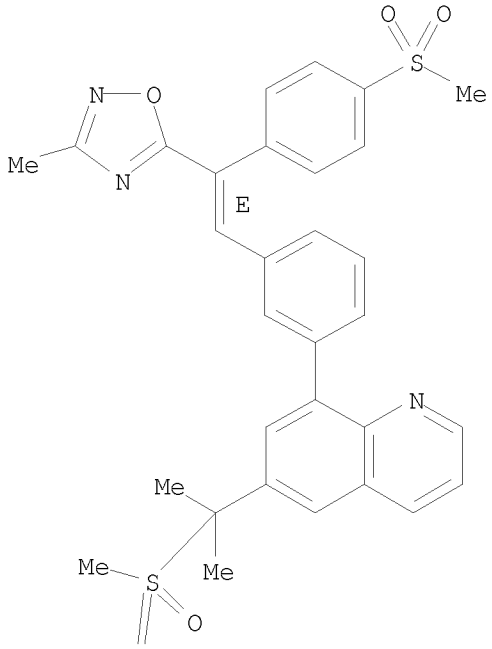


I

AB The discovery and SAR of a new series of substituted 8-arylquinoline PDE4 inhibitors are herein described. This work has led to the identification of several compds. with excellent in vitro and in vivo profiles, including a good therapeutic window of emesis to efficacy in several animal models. Typical optimized compds. from this series are potent inhibitors of PDE4 (IC50 < 1 nM) and also of LPS-induced TNF-α release in human whole blood (IC50 < 0.5 μM). The same compds. are potent inhibitors of ovalbumin-induced bronchoconstriction in conscious guinea pigs (EC50 < 0.1 mg/kg i.p.) but require a dose of about 10 mg/kg po in the squirrel monkey to produce an emetic response. From this series of compds., I (L-454,560) was identified as an optimized compound
IT 346629-30-9P, L 454,560 346629-32-1P
346629-43-4P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of functionalized 8-arylquinolines as potent and well tolerated PDE4 inhibitors)
RN 346629-30-9 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

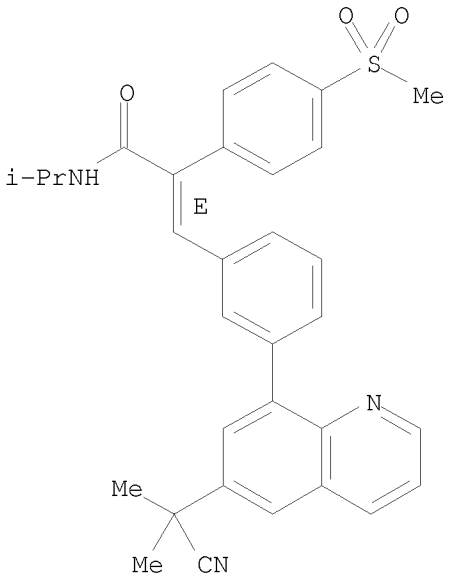
PAGE 1-A



PAGE 2-A

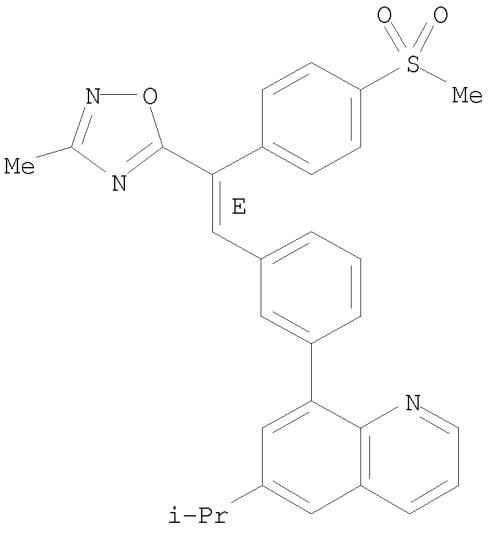
RN 346629-32-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-43-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



IT 346629-19-4P 346629-31-0P 346629-33-2P
346629-36-5P 346629-42-3P 346629-50-3P
871107-87-8P 871107-93-6P 871107-99-2P
871108-00-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of functionalized 8-arylquinolines as potent and well tolerated PDE4 inhibitors)
RN 346629-19-4 CAPLUS
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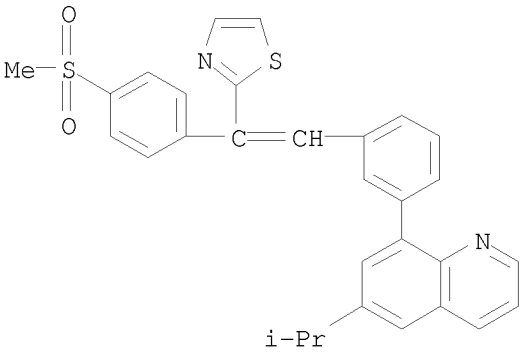
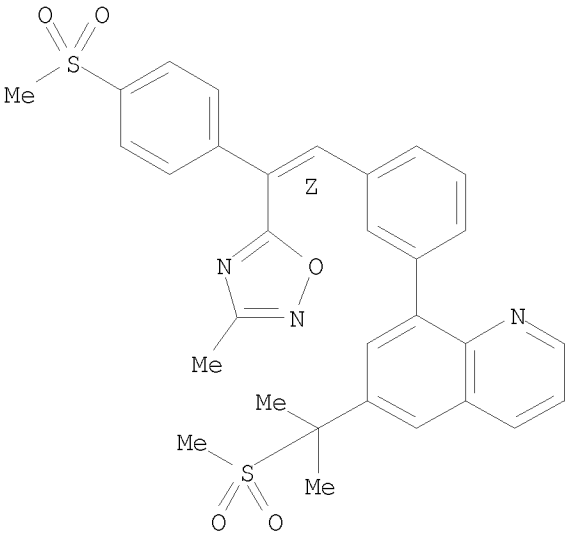
thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)



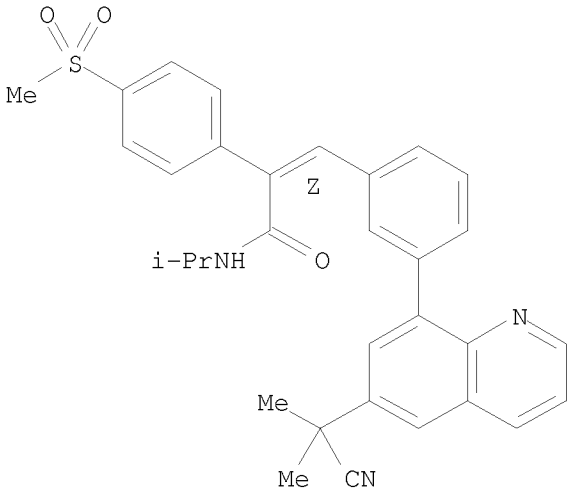
RN 346629-31-0 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-33-2 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)-, (αZ)- (CA INDEX NAME)

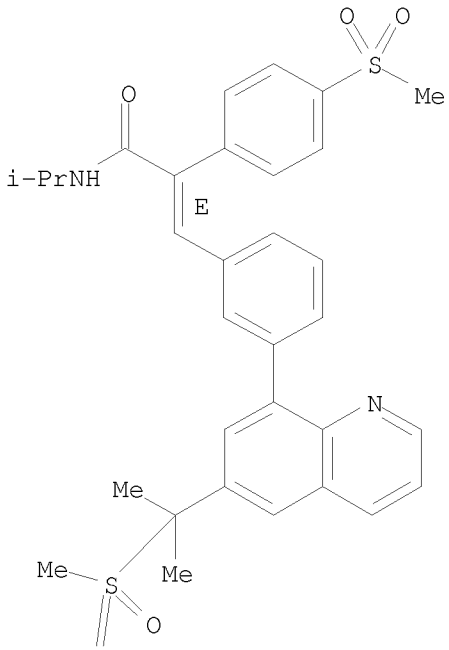
Double bond geometry as shown.



RN 346629-36-5 CAPLUS
CN Benzeneacetamide, N-(1-methylethyl)-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

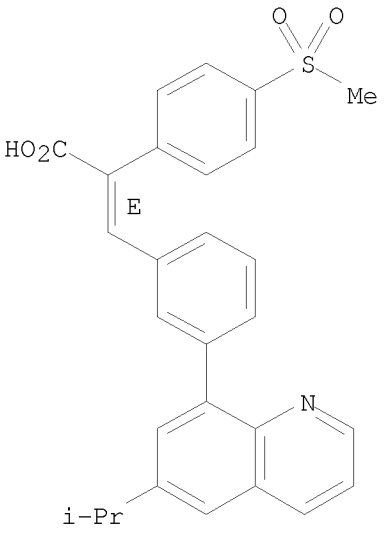
PAGE 1-A



PAGE 2-A

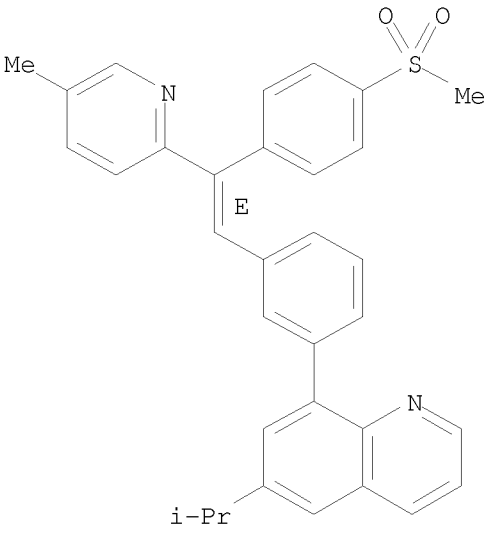
RN 346629-42-3 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



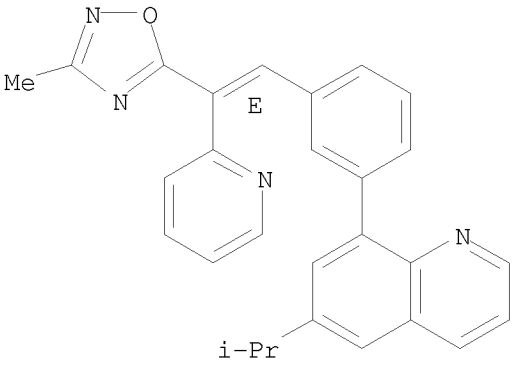
RN 346629-50-3 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



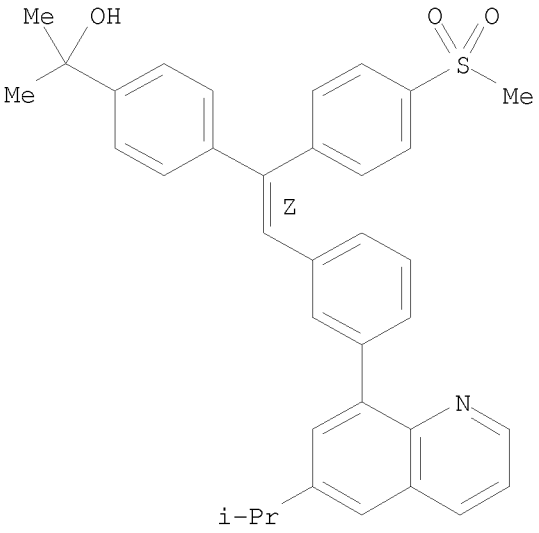
RN 871107-87-8 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-pyridinyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



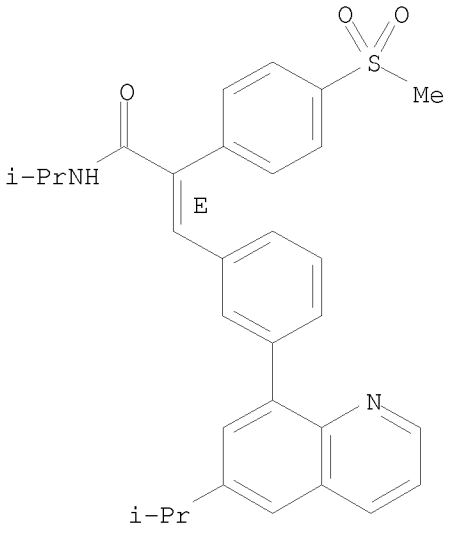
RN 871107-93-6 CAPLUS
CN Benzenemethanol, α,α-dimethyl-4-[(1Z)-2-[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.

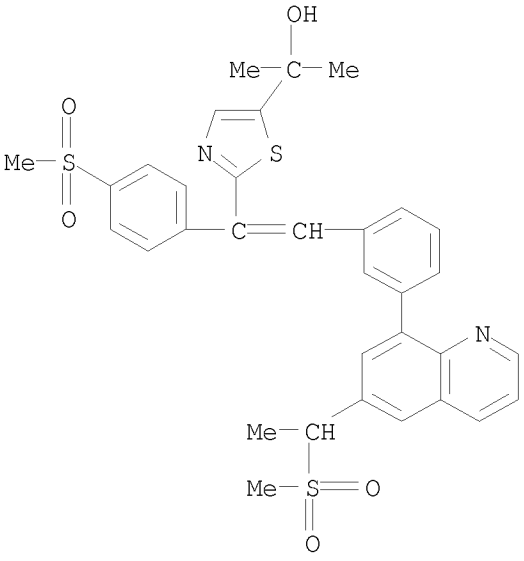


RN 871107-99-2 CAPLUS
CN Benzeneacetamide, N-(1-methylethyl)-α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



RN 871108-00-8 CAPLUS
CN 5-Thiazolemethanol, α,α-dimethyl-2-[2-[3-[6-[1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1059128 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 142:32997
TITLE: Use of phosphatase inhibitors as adjunct therapy for psychiatric disorders
INVENTOR(S): Scolnick, Edward M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004105698	A2	20041209	WO 2004-US16492	20040525
WO 2004105698	A3	20050602		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1633306	A2	20060315	EP 2004-753335	20040525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
US 20060258668	A1	20061116	US 2005-557648	20051118

PRIORITY APPLN. INFO.:
US 2003-474168P P 20030529
WO 2004-US16492 W 20040525

AB The use of a phosphatase inhibitor in conjunction with psychotherapy provides enhanced therapeutic results in the treatment of psychiatric disorders including, for example, specific phobias, panic disorders, anxiety disorders including posttraumatic stress disorders, and obsessive-compulsive disorder. The phosphatase that is inhibited can be calcineurin or protein phosphatase 1. Treatment with a phosphatase inhibitor can be combined with a phosphodiesterase 4 inhibitor.

IT 346629-17-2, 6-Isopropyl-8-[3-[(Z)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl]phenyl]quinoline 346629-20-7, 6-Isopropyl-8-[3-[(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-21-8, 6-Isopropyl-8-[3-[(Z)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-25-2, 2-Methyl-2-[8-[3-[(E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-quinolinyl]propanenitrile 346629-26-3, 6-[1-(Methylsulfonyl)ethyl]-8-[3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl]quinoline 346629-27-4, 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl]quinoline 346629-28-5, 8-[3-[(Z)-2-(1-Methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-(methylsulfonyl)ethyl]quinoline 346629-29-6, 8-[3-[(Z)-2-(1-Methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1'-methyl-1-(methylsulfonyl)ethyl]quinoline 346629-30-9, 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-32-1, (E)-3-[3-[6-(1-Cyano-1-methylethyl)-8-quinolinyl]phenyl]-N-isopropyl-2-[4-(methylsulfonyl)phenyl]-2-propenamide 346629-34-3, 8-[3-[(E)-2-[3-[(4-Methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline 346629-35-4, [5-[(E)-2-[3-[6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]-1,2,4-oxadiazol-3-yl]methanol 346629-36-5, (E)-N-Isopropyl-3-[3-[6-[1-methyl-1-

(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide 346629-39-8, 2-Methyl-2-[8-[3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-quinolinyl]propanenitrile 346629-40-1, (E)-3-[3-[6-(1-Cyano-1-methylethyl)-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide 346629-41-2, (E)-N-(tert-Butyl)-3-[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide 346629-42-3, (E)-3-[3-(6-Isopropyl-8-quinolinyl)phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid 346629-43-4, 6-Isopropyl-8-[3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-44-5, (E)-3-[3-[6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-2-propen-1-one 346629-45-6, (E)-N-Cyclopropyl-3-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide 346629-46-7, (E)-N-(tert-Butyl)-3-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide 346629-47-8, 8-[3-[2,2-Bis(4-chlorophenyl)vinyl]phenyl]-6-isopropylquinoline 346629-48-9, 6-Isopropyl-8-[3-[(E)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-50-3, 6-Isopropyl-8-[3-[(E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-52-5, 8-[3-[2,2-Bis[4-(methylsulfonyl)phenyl]vinyl]phenyl]-6-isopropylquinoline 346629-53-6, 2-Methyl-2-[8-[3-[(E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-quinolinyl]propanenitrile 346629-57-0, 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-59-2, 2-[6-[(E)-2-[3-[6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]-3-pyridinyl]-2-propanol 455948-57-9, (E)-3-[3-[6-(1-Cyano-1-methylethyl)-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid 455948-59-1, 2-[8-[3-[2,2-Bis[4-(methylsulfonyl)phenyl]vinyl]phenyl]-6-quinolinyl]-2-methylpropanenitrile 455948-60-4, 2-Methyl-2-[8-[3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridinyl)ethenyl]phenyl]-6-quinolinyl]propanenitrile 799804-04-9, 6-Isopropyl-8-[3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl]quinoline 799804-05-0, 2-[2-[(E)-2-[3-(6-Isopropyl-8-quinolinyl)phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]-1,3-thiazol-5-yl]-2-propanol 799804-06-1, 2-[8-[3-[(E)-2-[5-(1-Hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-quinolinyl]-2-methylpropanenitrile

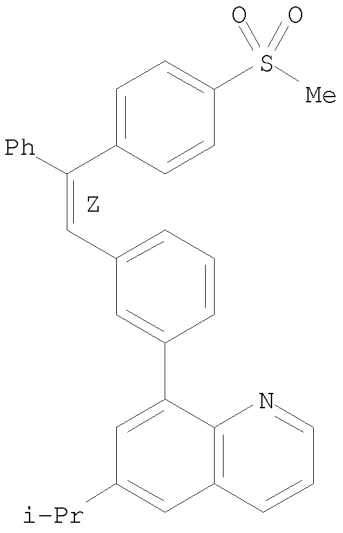
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(use of phosphatase inhibitors such calcineurin and protein phosphatase 1 as adjunct therapy for psychiatric disorders combined with phosphodiesterase 4 inhibitors)

RN 346629-17-2 CAPLUS

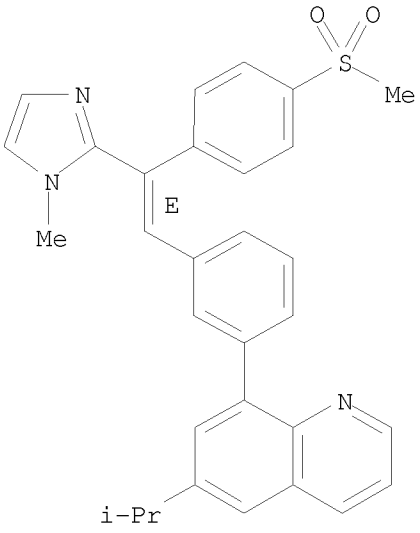
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1Z)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



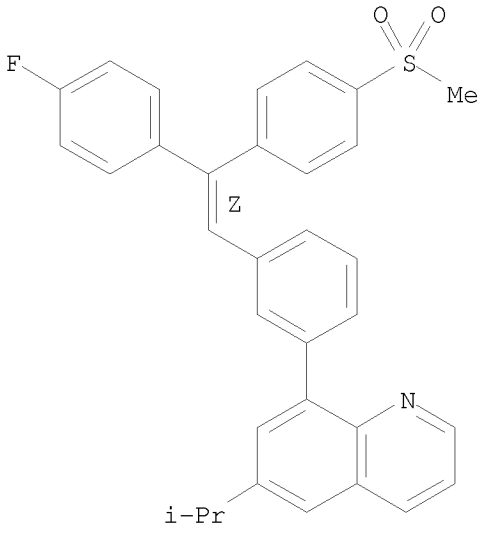
RN 346629-20-7 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



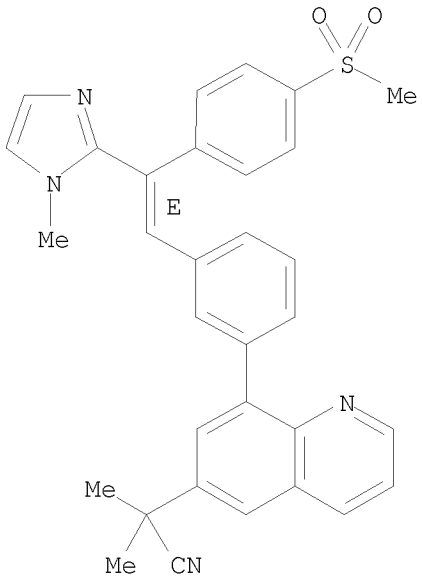
RN 346629-21-8 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)

Double bond geometry as shown.



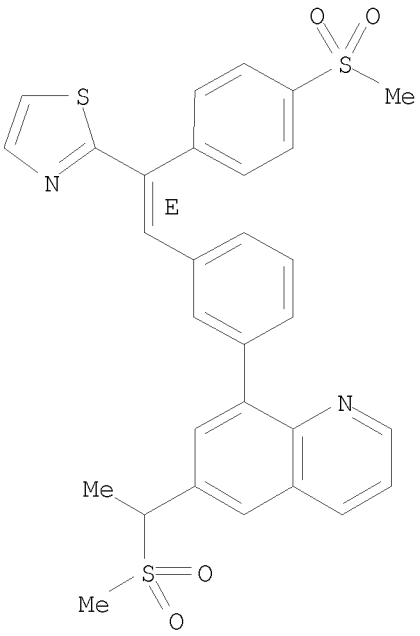
RN 346629-25-2 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



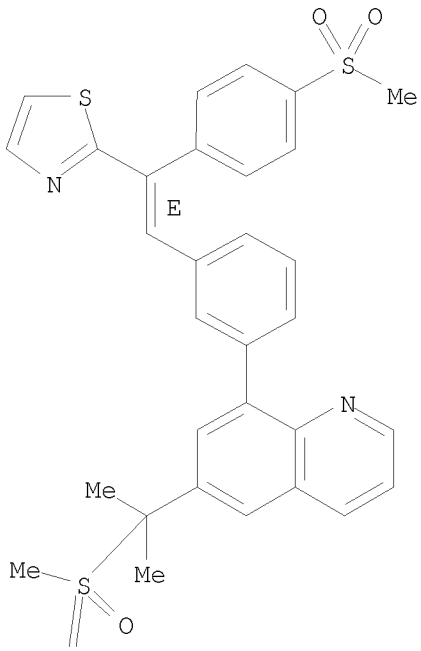
RN 346629-26-3 CAPLUS
CN Quinoline, 6-[1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



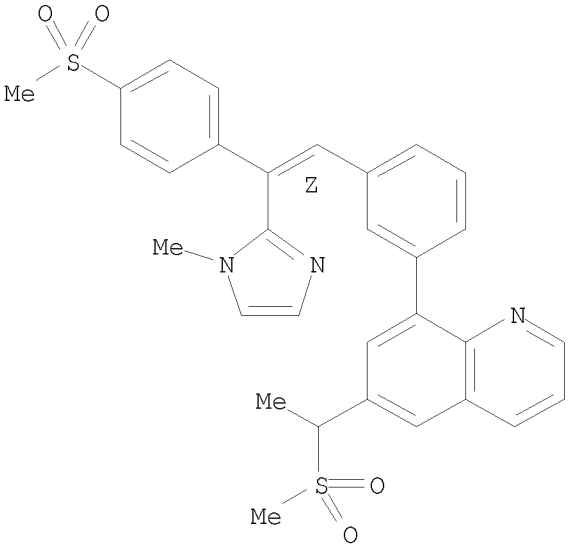
RN 346629-27-4 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



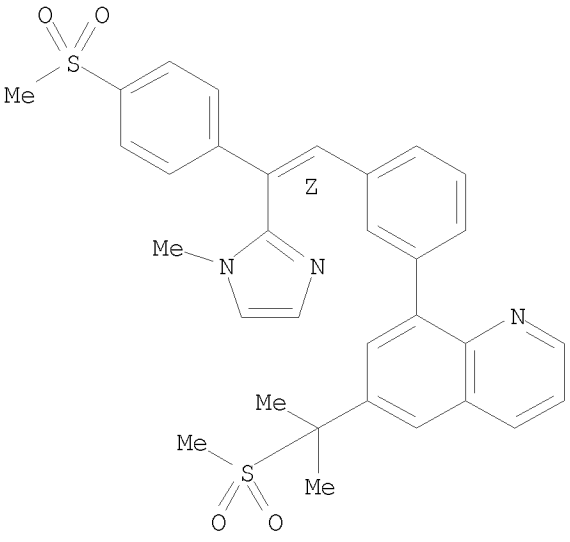
RN 346629-28-5 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-29-6 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-30-9 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

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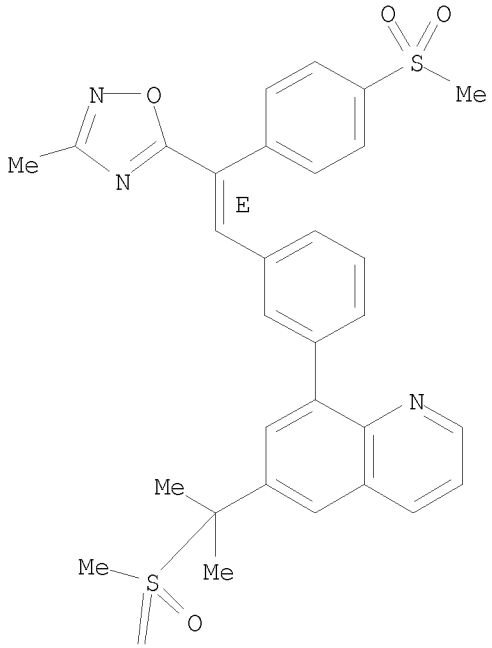
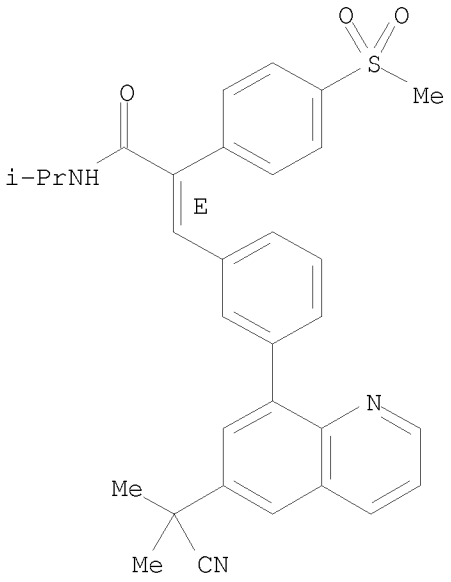


PAGE 2-A

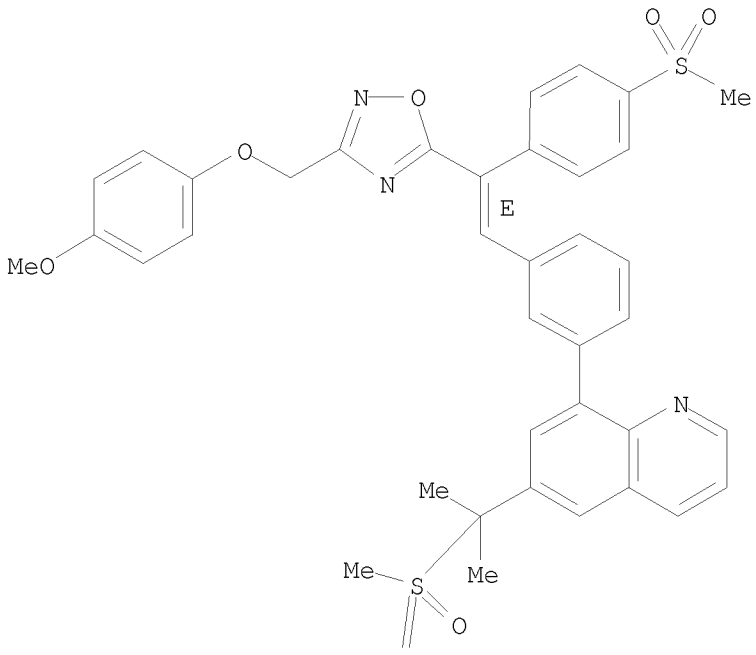
RN 346629-32-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-34-3 CAPLUS
CN Quinoline, 8-[3-[(1E)-2-[3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.

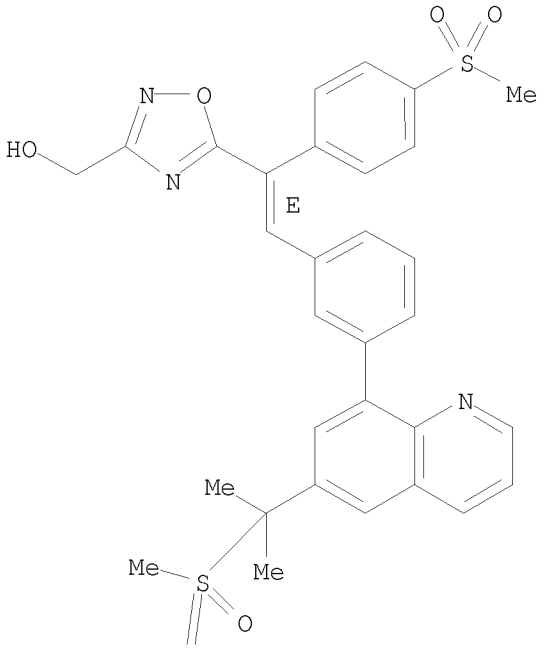


PAGE 2-A

RN 346629-35-4 CAPLUS
CN 1,2,4-Oxadiazole-3-methanol, 5-[(1E)-2-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

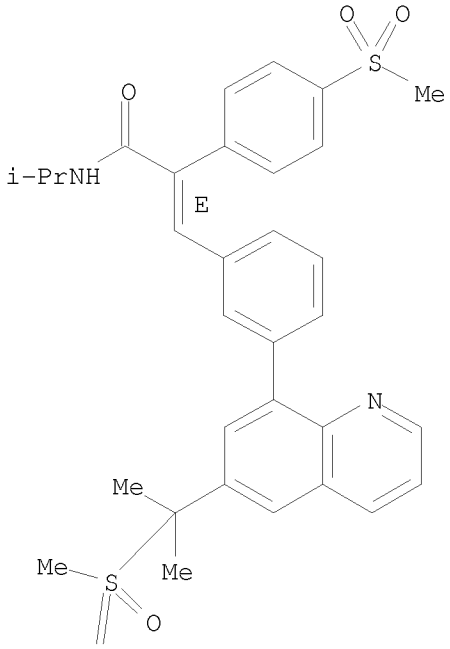


PAGE 2-A

RN 346629-36-5 CAPLUS
CN Benzeneacetamide, N-(1-methylethyl)-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

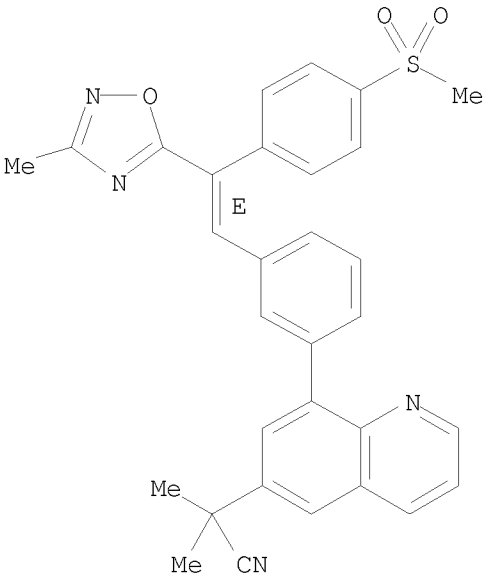
PAGE 1-A



PAGE 2-A

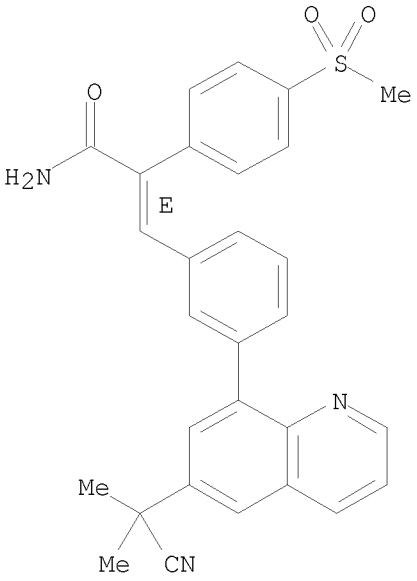
RN 346629-39-8 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



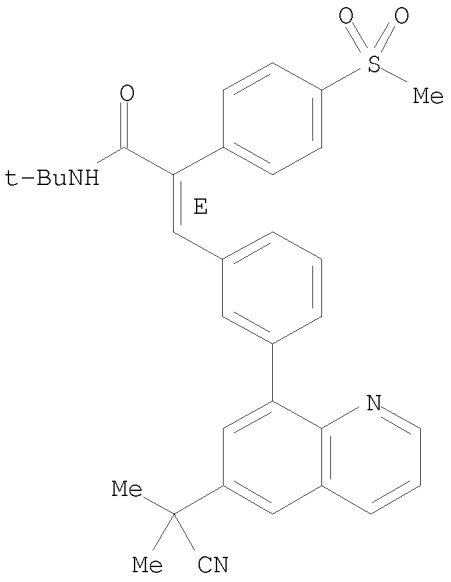
RN 346629-40-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



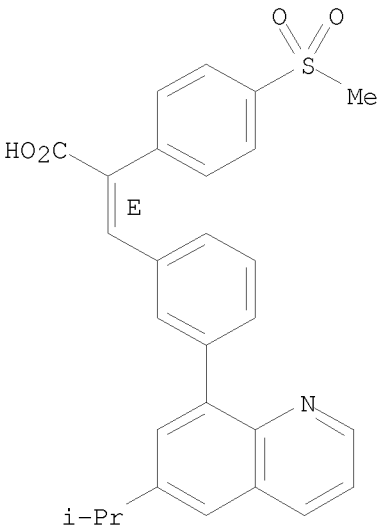
RN 346629-41-2 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1,1-dimethylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



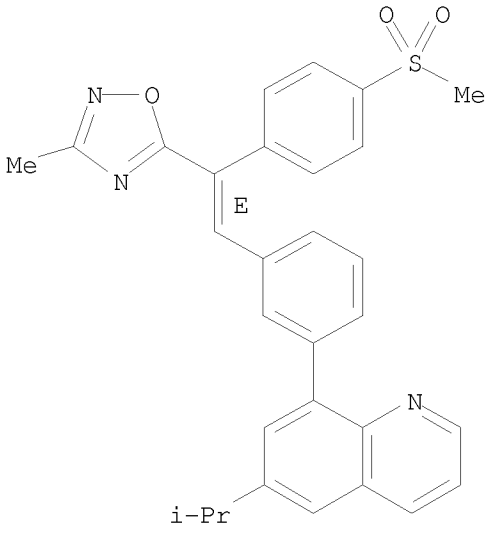
RN 346629-42-3 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



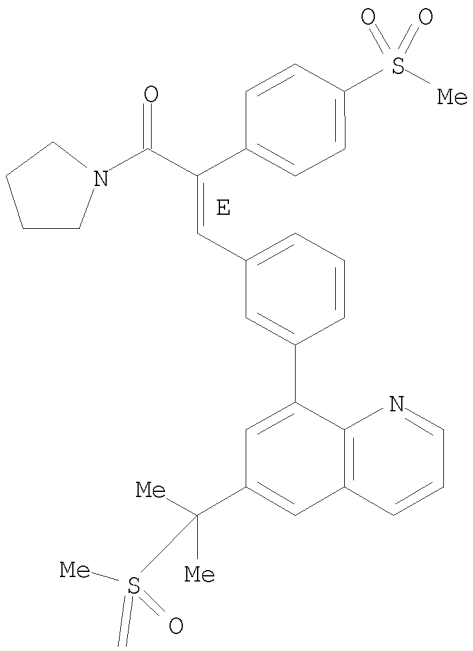
RN 346629-43-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-44-5 CAPLUS
CN 2-Propen-1-one, 3-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-, (2E)- (CA INDEX NAME)

Double bond geometry as shown.

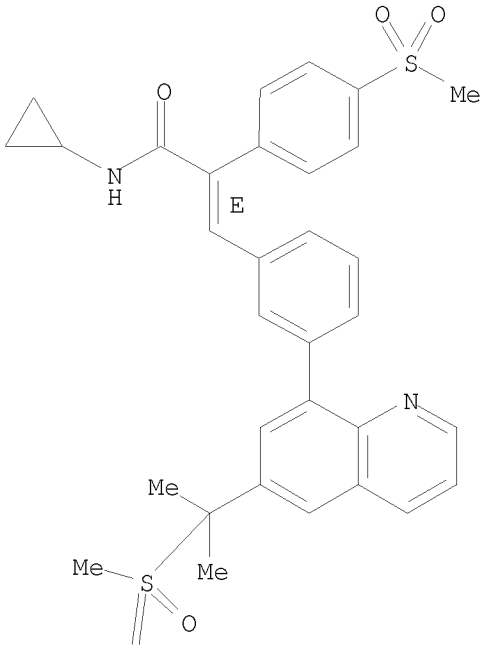


PAGE 2-A

RN 346629-45-6 CAPLUS
CN Benzeneacetamide, N-cyclopropyl-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

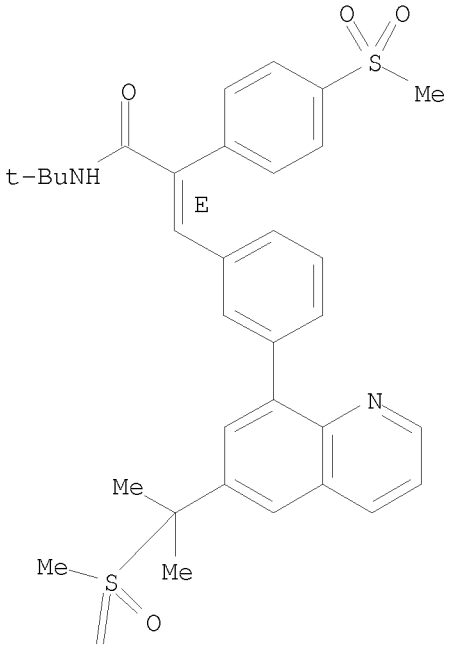


PAGE 2-A

RN 346629-46-7 CAPLUS
CN Benzeneacetamide, N-(1,1-dimethylethyl)-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

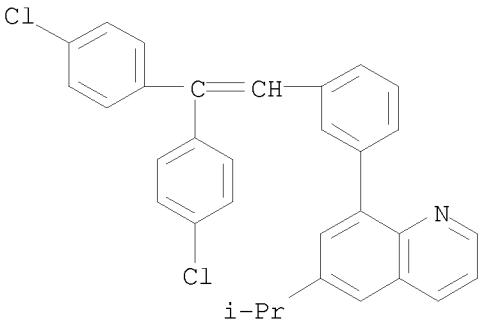
Double bond geometry as shown.

PAGE 1-A



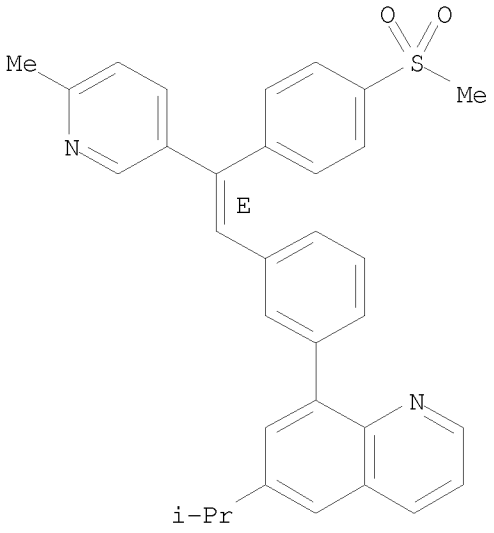
PAGE 2-A

RN 346629-47-8 CAPLUS
CN Quinoline, 8-[3-[2,2-bis(4-chlorophenyl)ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)



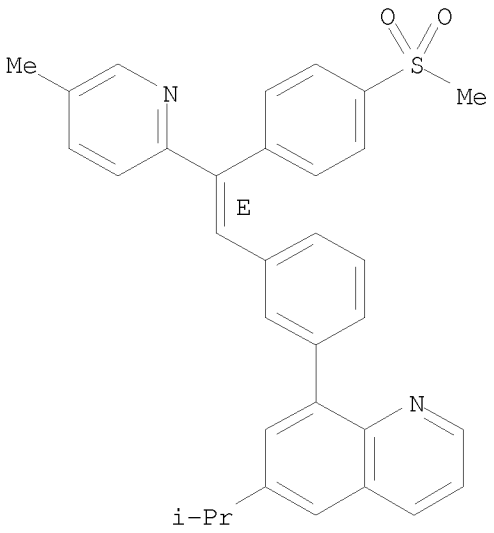
RN 346629-48-9 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

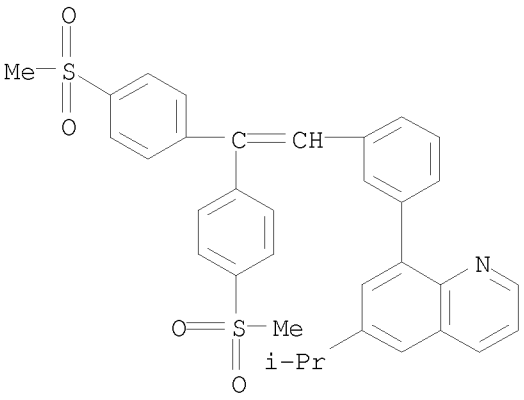


RN 346629-50-3 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

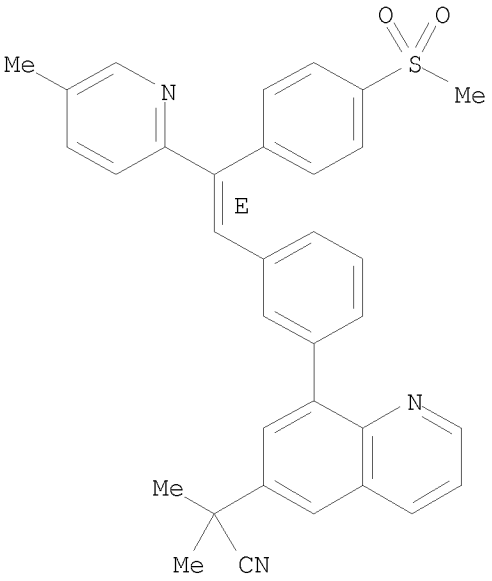


RN 346629-52-5 CAPLUS
CN Quinoline, 8-[3-[2,2-bis[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)



RN 346629-53-6 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

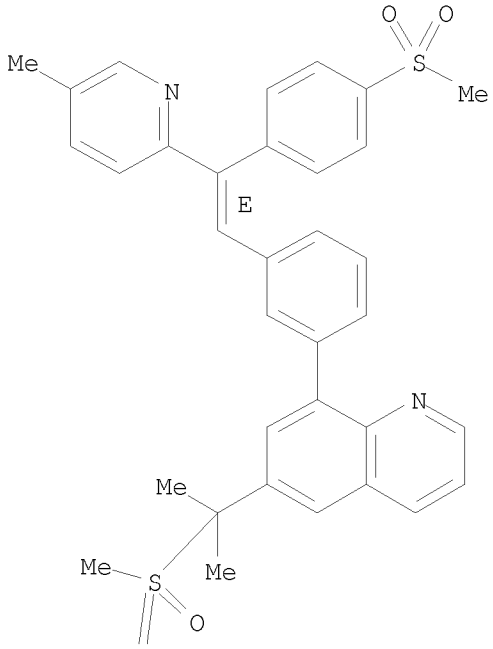
Double bond geometry as shown.



RN 346629-57-0 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

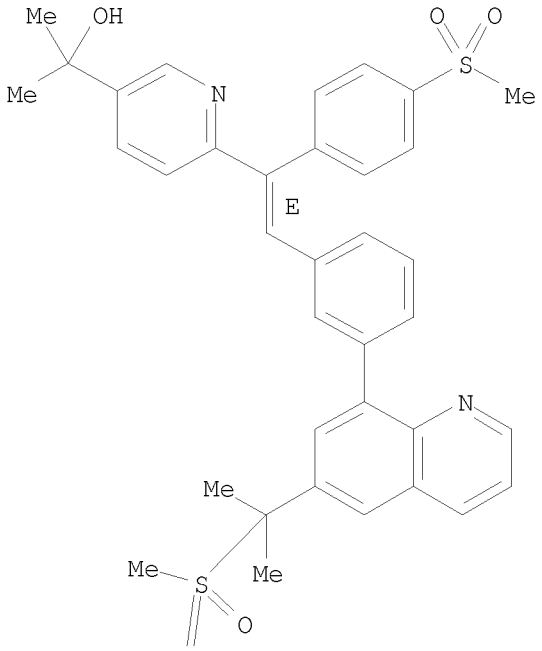


PAGE 2-A

RN 346629-59-2 CAPLUS
CN 3-Pyridinemethanol, α,α-dimethyl-6-[(1E)-2-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.

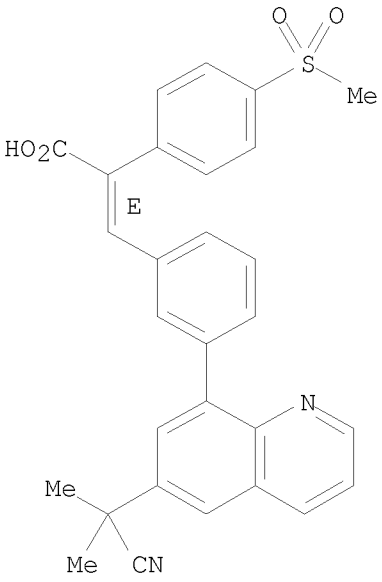
PAGE 1-A



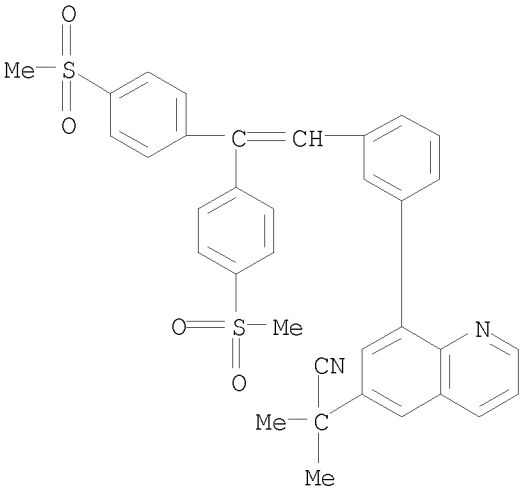
PAGE 2-A

RN 455948-57-9 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

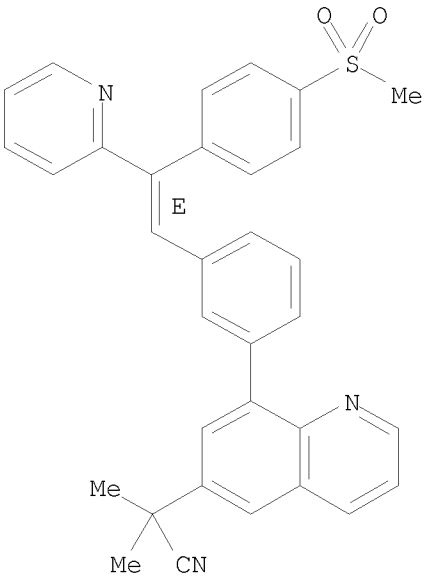


RN 455948-59-1 CAPLUS
CN 6-Quinolineacetonitrile, 8-[3-[2,2-bis[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-α,α-dimethyl- (CA INDEX NAME)



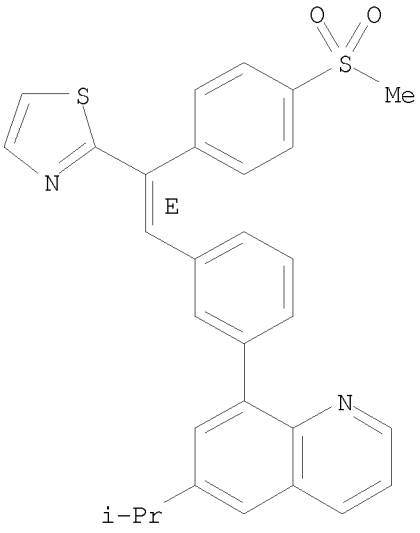
RN 455948-60-4 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridinyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



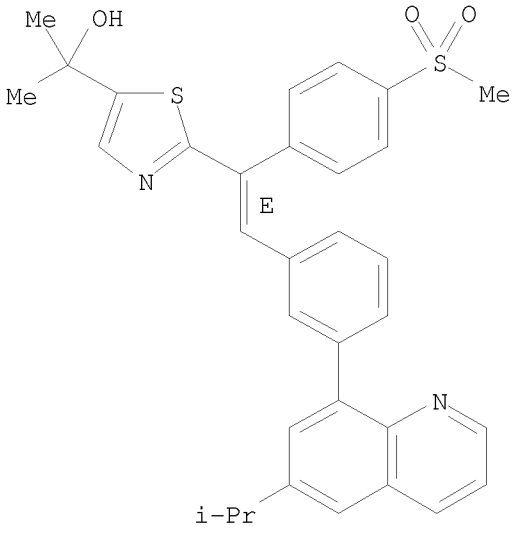
RN 799804-04-9 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



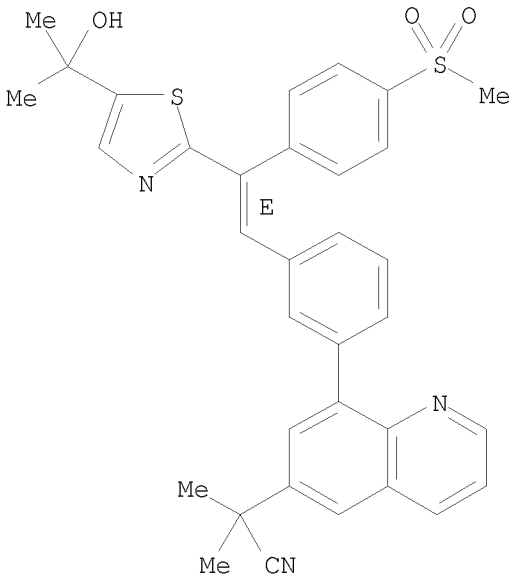
RN 799804-05-0 CAPLUS
CN 5-Thiazolemethanol, α,α-dimethyl-2-[(1E)-2-[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 799804-06-1 CAPLUS
CN 6-Quinolineacetonitrile, 8-[3-[(1E)-2-[5-(1-hydroxy-1-methylethyl)-2-thiazolyl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-α,α-dimethyl- (CA INDEX NAME)

Double bond geometry as shown.



L7 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:267275 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 140:303679
TITLE: Removal of an aldehyde impurity from a substituted 8-arylquinoline by treatment with a reactive polystyrene sulfonylhydrazine resin
INVENTOR(S): Biba, Mirlinda; Collins, Paul Compton; Welch, Christopher Joseph; Conlon, David A.; Drahus,

Antoinette
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004026794	A2	20040401	WO 2003-US28716	20030912
WO 2004026794	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2003272347	A1	20040408	AU 2003-272347	20030912
EP 1545526	A2	20050629	EP 2003-754525	20030912
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 20070054941	A1	20070308	US 2005-526782	20050304
PRIORITY APPLN. INFO.:			US 2002-411245P P	20020917
			WO 2003-US28716 W	20030912

OTHER SOURCE(S): MARPAT 140:303679
GI

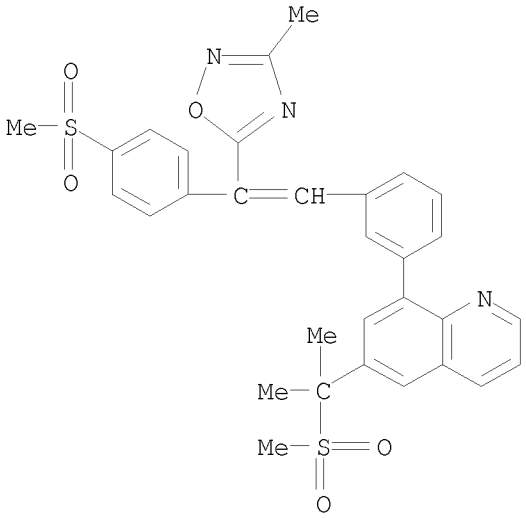
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A purification method of a substituted 8-arylquinoline (I) utilizes contacting the I with a DMF-swelled polystyrene-based sulfonylhydrazine reactive resin to remove the 8-(3-formylphenyl)quinoline impurity (II).

IT 676323-87-8P
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(removal of an aldehyde impurity from a substituted 8-arylquinoline by treatment with a reactive polystyrene sulfonylhydrazine resin)

RN 676323-87-8 CAPLUS

CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)



L7 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:22685 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 138:73184
TITLE: Preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors
INVENTOR(S): Dube, Daniel; Girard, Yves; MacDonald, Dwight; Mastracchio, Anthony; Gallant, Michel; Lacombe, Patrick; Deschenes, Denis
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003002118	A1	20030109	WO 2002-CA953	20020626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2450686	A1	20030109	CA 2002-2450686	20020626
AU 2002344885	A1	20030303	AU 2002-344885	20020626
AU 2002344885	B2	20060629		
EP 1404330	A1	20040407	EP 2002-742600	20020626
EP 1404330	B1	20050601		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005501822	T	20050120	JP 2003-508357	20020626
AT 296630	T	20050615	AT 2002-742600	20020626
ES 2242036	T3	20051101	ES 2002-742600	20020626
US 20040162314	A1	20040819	US 2003-478791	20031125

US 6919353 B2 20050719

PRIORITY APPLN. INFO.: US 2001-301220P P 20010627
US 2001-303472P P 20010706
WO 2002-CA953 W 20020626

OTHER SOURCE(S): MARPAT 138:73184

GI

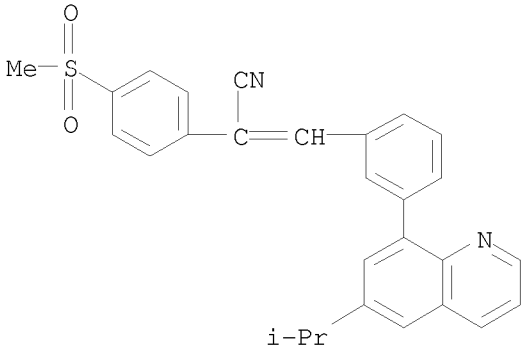
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 8-Arylquinolines (shown as I; variables defined below; e.g. both enantiomers of 4-hydroxy-1-[3-[6-(1-methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)-4-methylpentan-3-one) wherein the aryl group at the 8-position contains a meta two atom bridge to an optionally substituted Ph or pyridyl group, are PDE4 inhibitors useful to treat asthma, chronic bronchitis, chronic obstructive pulmonary disease, arthritis, respiratory distress syndrome, allergic rhinitis, neurogenic inflammation, pain, rheumatoid arthritis, and other diseases. R1-R7 and Ar are as in claim 1. For I: Ar is Ph, pyridinone, pyridyl, or pyridyl N-oxide, optionally substituted with 1-5 independent -C1-6-alkyl, -OH, -CN, halogen, -CF3, -(C0-6-alkyl)-SOn-(C1-6-alkyl), -(C0-6-alkyl)-SOn-NH-(C1-6-alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N, wherein the 5-membered-ring is optionally substituted. R1 is H, halogen; or a -C1-6-alkyl, -cycloC3-6alkyl, -C1-6-alkenyl, -C0-4alkyl-C(O)-C0-4alkyl, -C1-6-alkoxy, aryl, heteroaryl, -CN, -heterocycloC3-6-alkyl, -amino, -C1-6-alkylamino, -(C1-6-alkyl)(C1-6-alkyl)amino, -C1-6-alkyl(oxy)C1-6-alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SOnNH(aryl), -SOnNH(heteroaryl), -SOnNH(C1-6-alkyl), -C(O)N(C0-6alkyl)(C0-6-alkyl), -NH-SOn-(C1-6-alkyl), -carbamoyl, -(C1-6-alkyl)-O-C(CN)dialkylamino, or -(C0-6-alkyl)-SOn-(C1-6-alkyl) group, wherein any of the groups is optionally substituted with = 1-5 substituents. R2, R3, R6, and R7 = H, halogen, hydroxy, -C1-6-alkyl, or -C1-6-alkoxy, wherein the alkyl and alkoxy are optionally substituted independently with 1-3 halogen or OH; R4 is H, halogen, -CN, Ph, oxadiazolyl, or -C(O)-O-C0-6alkyl, wherein the alkyl and latter three possibilities are optionally substituted. R5 is H, hydroxy, -CN; or a -C1-6-alkyl, -C(O)C1-6alkyl, -C(O)aryl, -C(O)pyridyl, -C(O)-O-C0-6-alkyl, -C(O)-C3-7-cycloalkyl, -C1-6-alkyl-C3-7cycloalkyl, -C1-6-alkyl(C3-7-cycloalkyl)2, -C1-6-alkylaryl, -C(O)-N(C0-6alkyl)2, -SOnaryl, -SOn-C1-6-alkyl, -SOn-C3-7-cycloalkyl, -SOn-N(C0-6-alkyl)2, -P(O)(C1-6-alkyl)2, -P(O)(C1-6-alkoxy)2, Ph, pyridyl, -SOnimidazolyl, -SOnthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms = O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted; or R5 and R6 form :O; or R6 and R3 form -CH2- or -O-; and n is 0-2. Although the methods of preparation are not claimed, >100 example prepns. are included. The IC50 values for PDE4 inhibition of Examples 1-113 generally are 0.02-26 μM as measured using LPS and FMLP-induced TNF-α and LTB4 assays in human whole blood. I were tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs;. Administration of I (0.001-10 mg/kg i.p. or p.o.), up to three times during the 48 h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with I. Compds. which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format; IC50 values of I generally ranged 0.1-25 nM.

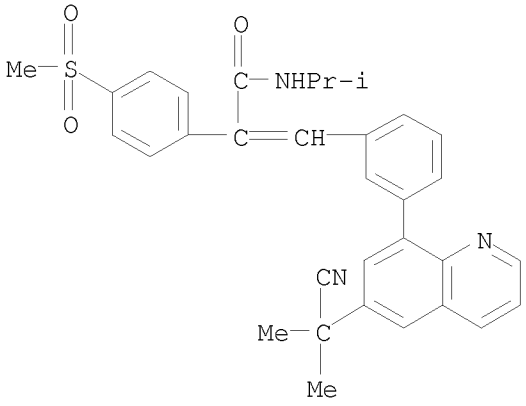
IT 481680-70-0P, 3-[3-(6-Isopropylquinolin-8-yl)phenyl]-2-[4-(methylsulfonyl)phenyl]prop-2-enenitrile 481680-74-4P,

3-[3-[6-(Cyanodimethylmethyl)quinolin-8-yl]phenyl]-N-isopropyl-2-(4-methanesulfonylphenyl)acrylamide 481680-96-0P, 3-[3-[6-(1-Methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)acrylic acid 481680-97-1P, 3-[3-[6-(1-Methanesulfonyl-1-methylethyl)quinolin-8-yl]phenyl]-2-(4-methanesulfonylphenyl)acrylic acid methyl ester 481681-05-4P, 8-[4-Fluoro-3-[2-(4-methanesulfonylphenyl)vinyl]phenyl]-6-isopropylquinoline 481681-15-6P, 3-[3-(6-Isopropylquinolin-8-yl)phenyl]-2-pyridin-4-ylacrylonitrile
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted 8-arylquinoline phosphodiesterase-4 (PDE4) inhibitors)

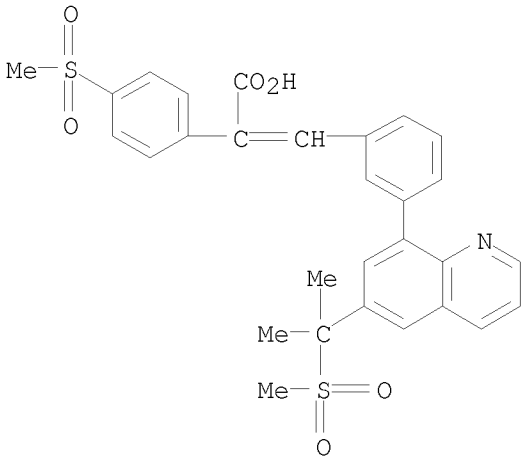
RN 481680-70-0 CAPLUS
CN Benzeneacetonitrile, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)- (CA INDEX NAME)



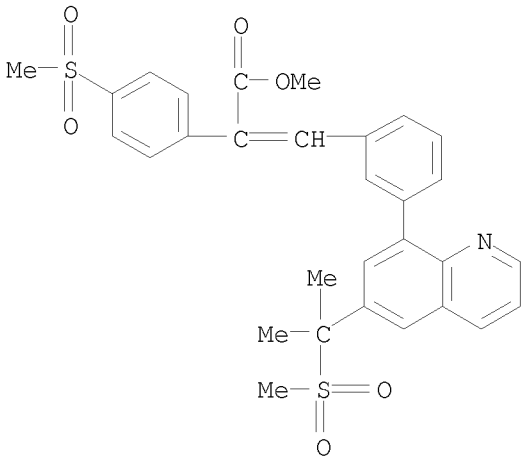
RN 481680-74-4 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)- (CA INDEX NAME)



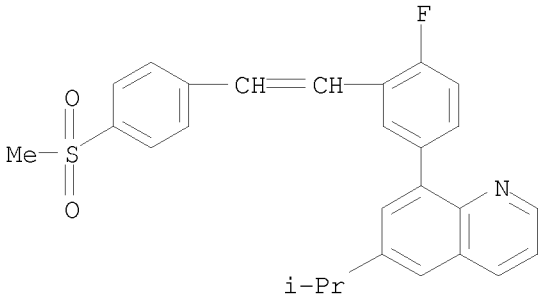
RN 481680-96-0 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)- (CA INDEX NAME)



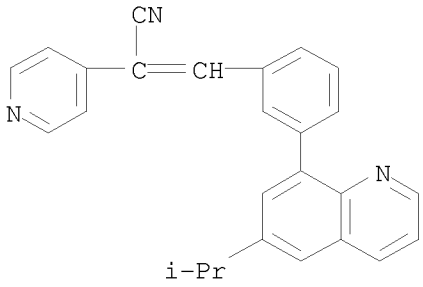
RN 481680-97-1 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, methyl ester (CA INDEX NAME)



RN 481681-05-4 CAPLUS
CN Quinoline, 8-[4-fluoro-3-[2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)



RN 481681-15-6 CAPLUS
CN 4-Pyridineacetonitrile, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

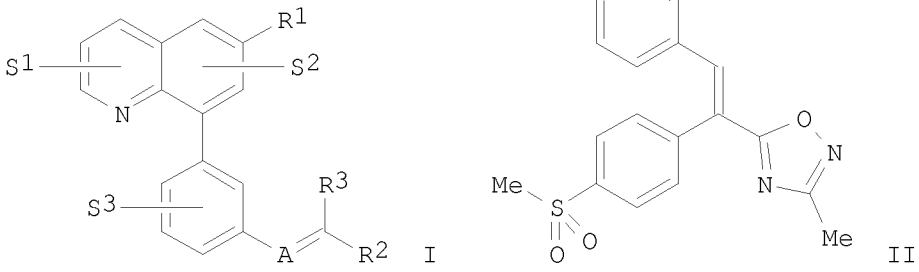
L7 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:695783 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 137:216886
TITLE: Preparation of 8-(alkenylaryl)quinoline phosphodiesterase-4 inhibitors
INVENTOR(S): Vailaya, Anant; Conlon, David A.; Ho, Guo-Jie; Macdonald, Dwight; Perrier, Helene; Thibert, Roch; Kwong, Elizabeth; Clas, Sophie-Dorothee
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Merck Frosst Canada & Co.
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069970	A1	20020912	WO 2001-US48674	20011214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20020143032	A1	20021003	US 2001-40993	20011109
US 6740666	B2	20040525		
CA 2431549	A1	20020912	CA 2001-2431549	20011214
AU 2001297603	A1	20020919	AU 2001-297603	20011214
AU 2001297603	B2	20060216		
EE 200300266	A	20031015	EE 2003-266	20011214
EP 1363635	A1	20031126	EP 2001-273908	20011214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016372	A	20031209	BR 2001-16372	20011214
HU 2004000654	A2	20040628	HU 2004-654	20011214

JP 2004521921	T	20040722	JP 2002-569145		20011214
CN 1551769	A	20041201	CN 2001-822760		20011214
NZ 526376	A	20050225	NZ 2001-526376		20011214
BG 107900	A	20040630	BG 2003-107900		20030611
ZA 2003004672	A	20040421	ZA 2003-4672		20030617
NO 2003002807	A	20030815	NO 2003-2807		20030619
MX 2003PA05673	A	20031006	MX 2003-PA5673		20030619
IN 2003CN01089	A	20050422	IN 2003-CN1089		20030717
PRIORITY APPLN. INFO.:			US 2000-256803P	P	20001220
			WO 2001-US48674	W	20011214

OTHER SOURCE(S): MARPAT 137:216886

GI



AB Title compds. I [wherein S1-S3 = independently H, OH, halo, NO2, CN, or (un)substituted alkyl or alkoxy; R1 = H, OH, halo, or (un)substituted acyl, (cyclo)alkyl, alkenyl, alkoxy, (hetero)aryl, heterocycloalkyl, NH2, carbamoyl, sulfamoyl , etc.; A = CH, C-ester, or CR4; R2 and R3 = independently H, halo, CN, CO2H, or (un)substituted (hetero)aryl, (heterocyclo)alkyl, alkoxy, acyl, carbamoyl, etc.; with the proviso that 1 of R2 and R3 must = (hetero)aryl; when R2 and R2 both = (hetero)aryl, then R2 and R3 may be optionally connected by a thio, oxy, or alkyl bridge to from a fused 3-ring system; R4 = CN or (un)substituted (hetero)aryl, alkyl, acyl, carbamoyl, etc.; or R2 or R3 may be optionally joined to R4 by a bond to form a ring; n = 0-2; and pharmaceutically acceptable H2SO4, methanesulfonic acid, p-toluenesulfonic acid, 2-naphthalenesulfonic acid, hydrochloride acid, or benzenesulfonic acid salts thereof] were prepared as phosphodiesterase-4 (PDE4) inhibitors. For example, a solution of (E)-1-(3-bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethene, diboron pinacol ester, [1,1'-bis(diphenylphosphino)ferrocene]PdCl2, and KOAc in DMF was stirred at 80° for 3 h. Sequential addition of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-bromoquinoline, [1,1'-bis(diphenylphosphino)ferrocene]PdCl2, and Na2CO3 followed by heating at 80° overnight gave (E)- and (Z)-II. Forty-two compds. of the invention exhibited IC50 values ranging from 0.04 μM to 8.71 μM in LPS and fMLP-induced TNF-α and LTB4 assays performed on human whole blood. All but one of same compds. inhibited the hydrolysis of cAMP to AMP by type-IV cAMP-specific phosphodiesterases with IC50 values ranging from 0.14 nM to 10.24 nM. Thus, I are useful as anti-inflammatory and

anti-allergic agents for treatment of a wide variety of PDE4-related diseases and conditions (no data).

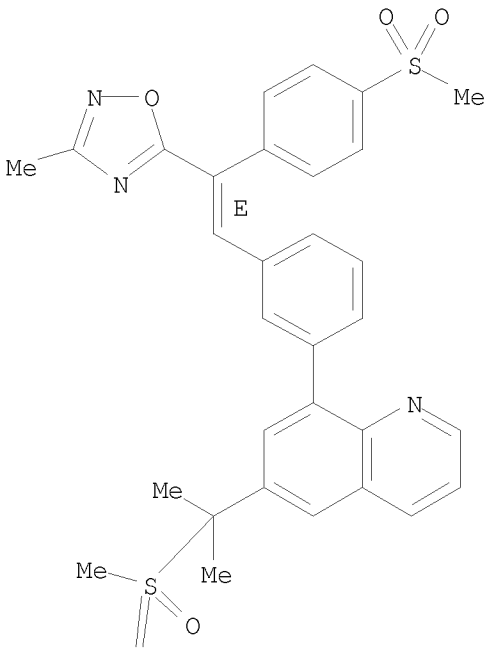
IT 346629-30-9P, 6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-[3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline 346629-34-3P, 8-[3-[(E)-2-[3-[(4-Methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(PDE4 inhibitor; preparation of (alkenylaryl)quinoline phosphodiesterase-4 inhibitors with anti-inflammatory and anti-allergic activity)

RN 346629-30-9 CAPLUS

CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



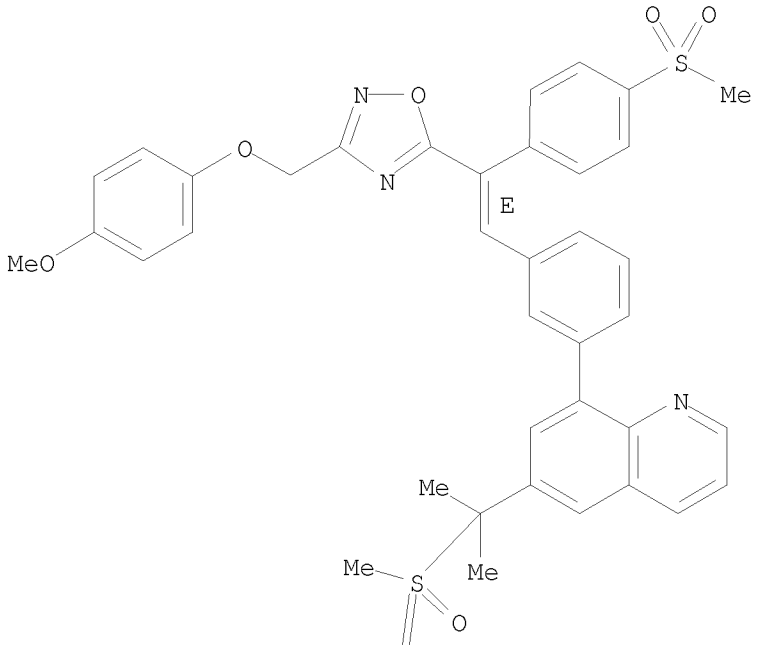
PAGE 2-A

RN 346629-34-3 CAPLUS

CN Quinoline, 8-[3-[(1E)-2-[3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.

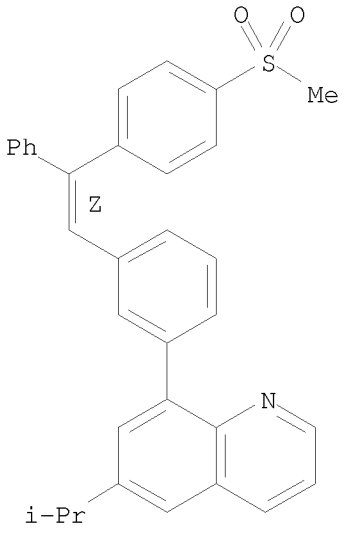
PAGE 1-A



PAGE 2-A

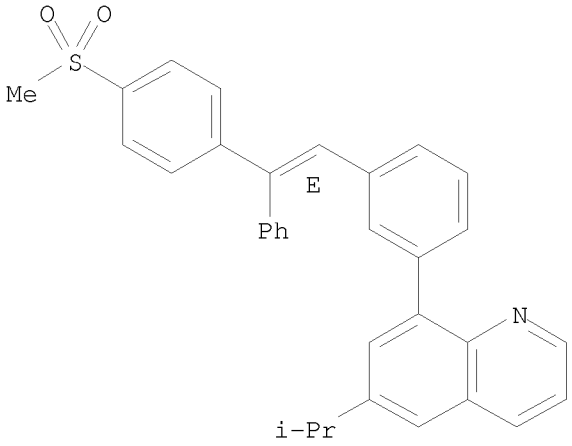
IT 346629-17-2P, 6-Isopropyl-8-[3-[(Z)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl]phenyl]quinoline 346629-18-3P, 6-Isopropyl-8-[3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-

Double bond geometry as shown.

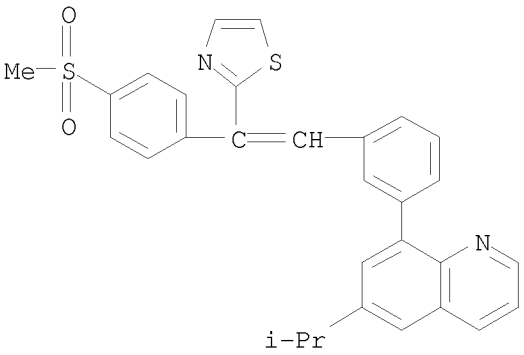


RN 346629-18-3 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

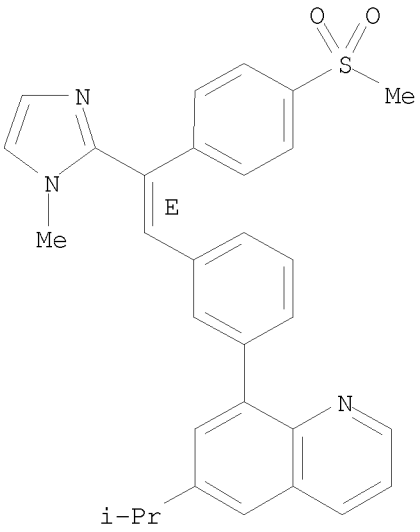


RN 346629-19-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)



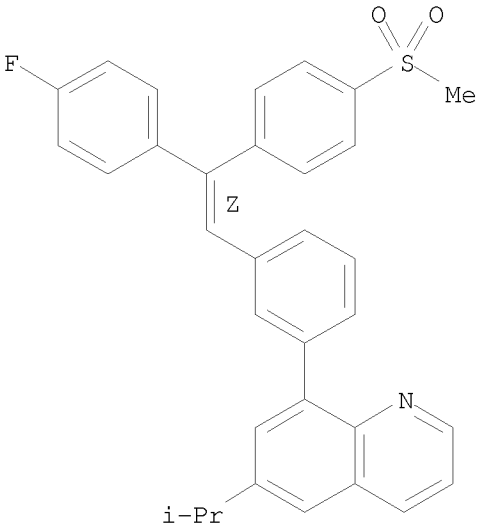
RN 346629-20-7 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



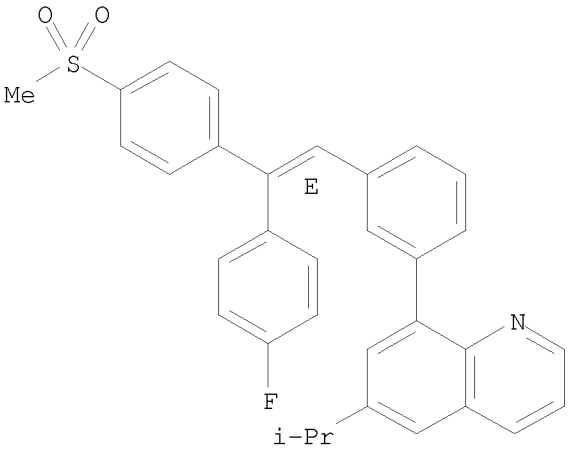
RN 346629-21-8 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)

Double bond geometry as shown.

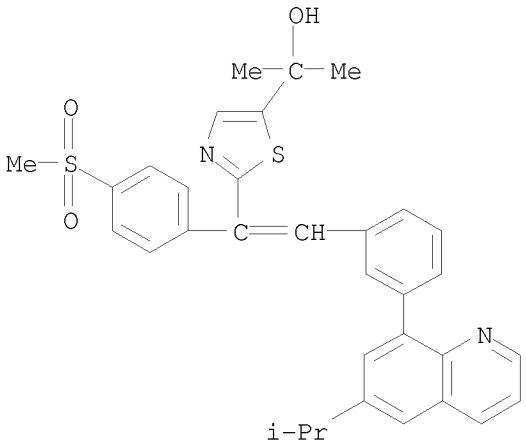


RN 346629-22-9 CAPLUS
CN Quinoline, 8-[3-[(1E)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)

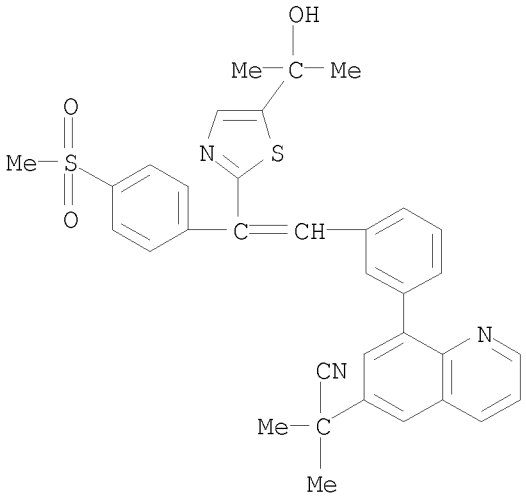
Double bond geometry as shown.



RN 346629-23-0 CAPLUS
CN 5-Thiazolemethanol, α,α-dimethyl-2-[2-[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

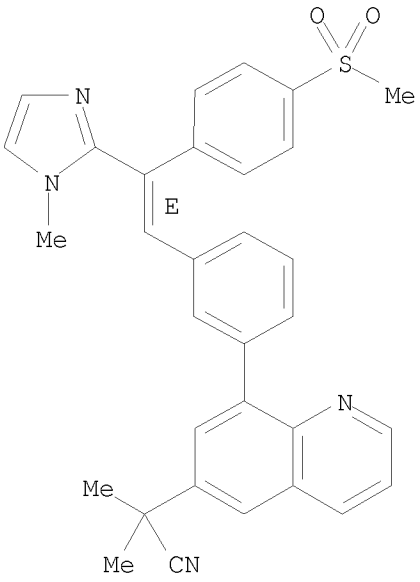


RN 346629-24-1 CAPLUS
CN 6-Quinolineacetonitrile, 8-[3-[2-[5-(1-hydroxy-1-methylethyl)-2-thiazolyl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-α,α-dimethyl- (CA INDEX NAME)



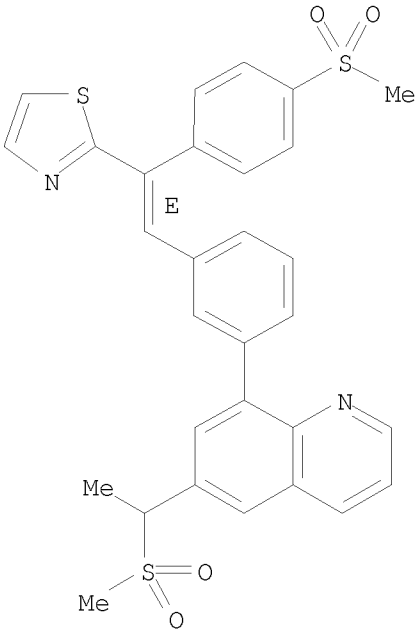
RN 346629-25-2 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-26-3 CAPLUS
CN Quinoline, 6-[1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-27-4 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

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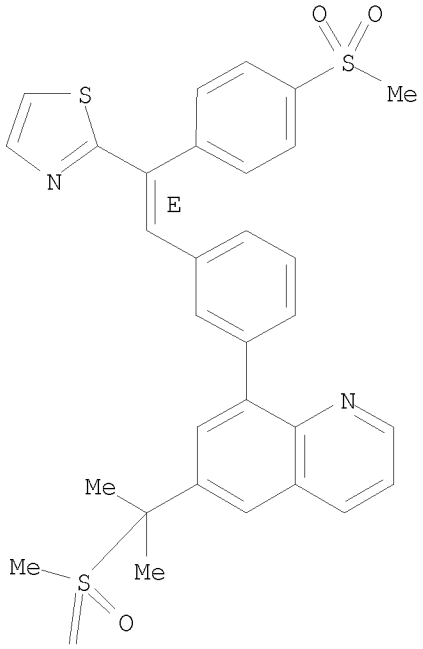
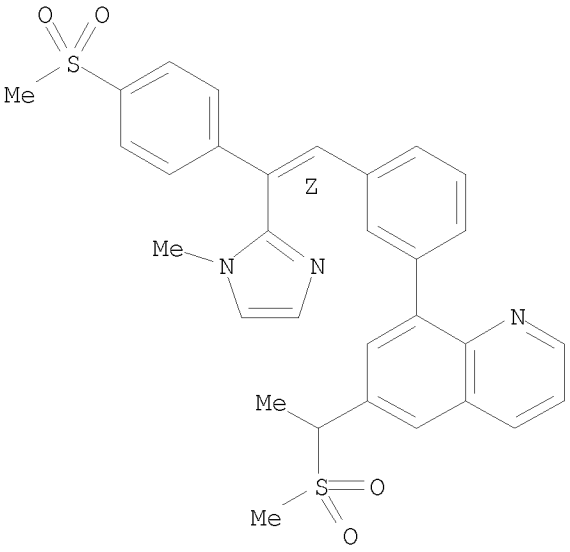


PAGE 2-A

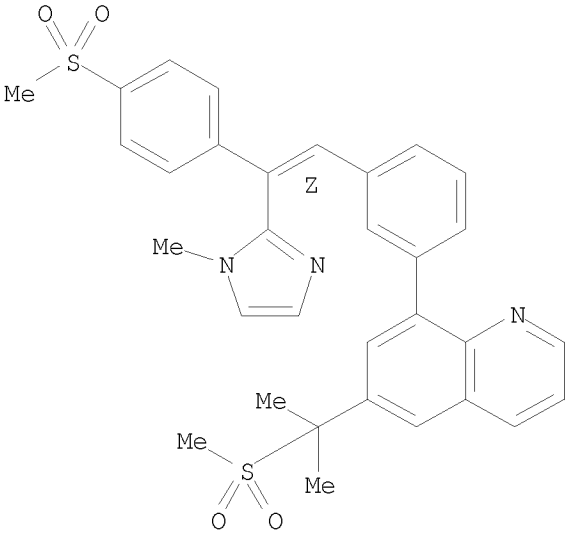
RN 346629-28-5 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.



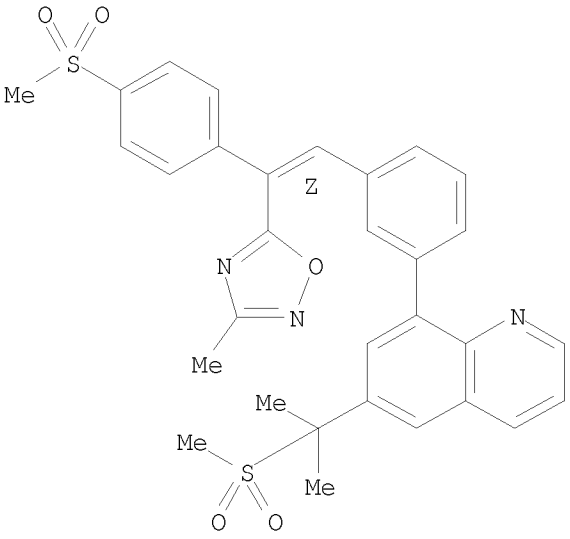
RN 346629-29-6 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.



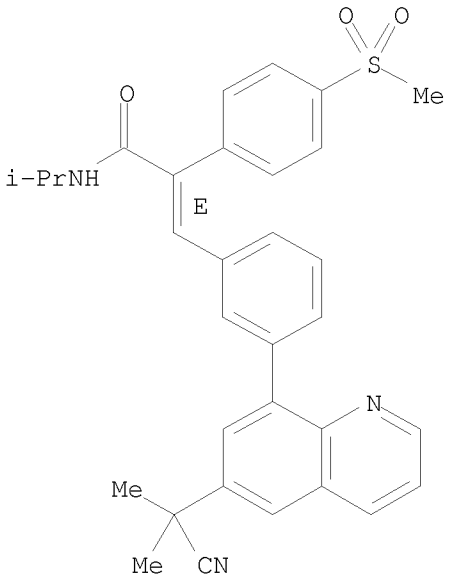
RN 346629-31-0 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-32-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

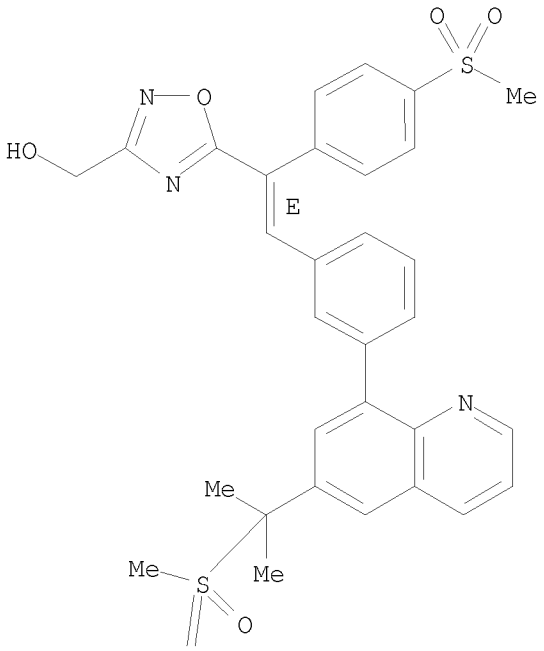
Double bond geometry as shown.



RN 346629-35-4 CAPLUS
CN 1,2,4-Oxadiazole-3-methanol, 5-[(1E)-2-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

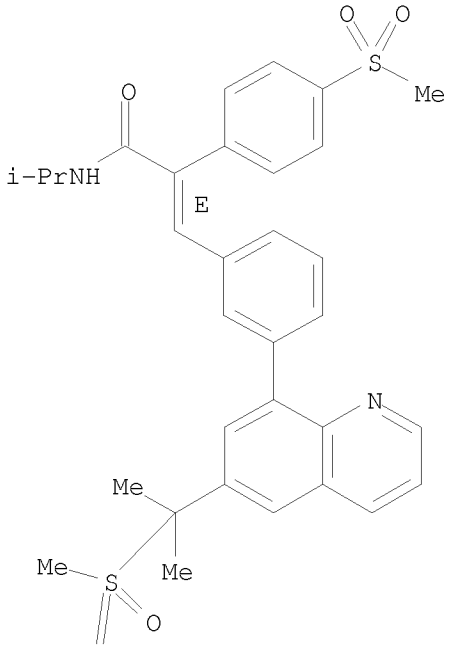


PAGE 2-A

RN 346629-36-5 CAPLUS
CN Benzeneacetamide, N-(1-methylethyl)-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

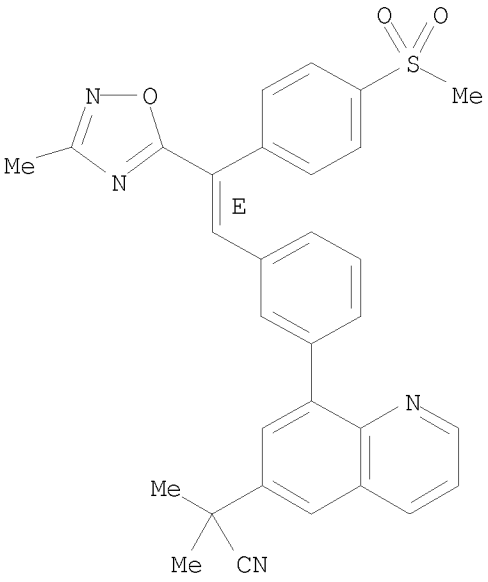
PAGE 1-A



PAGE 2-A

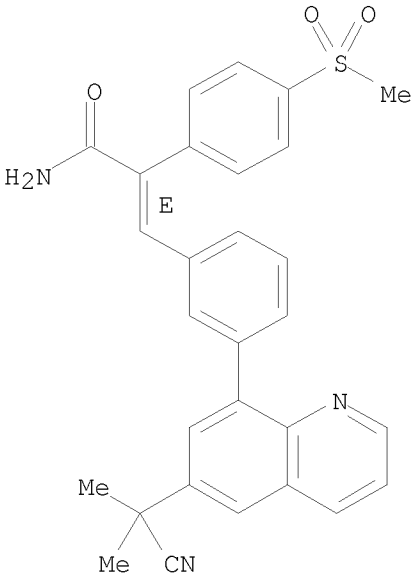
RN 346629-39-8 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



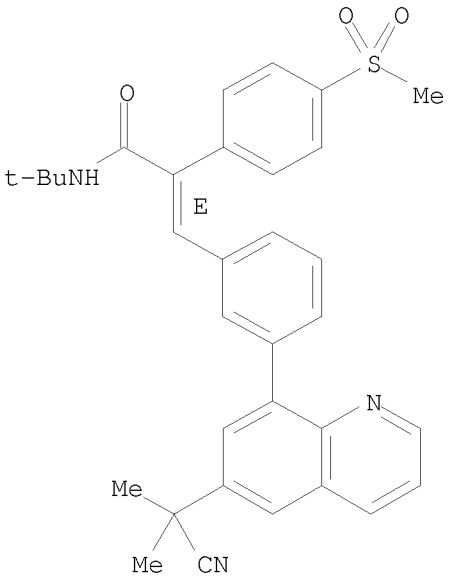
RN 346629-40-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



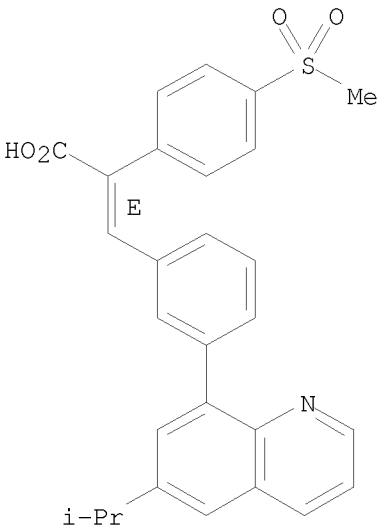
RN 346629-41-2 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1,1-dimethylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



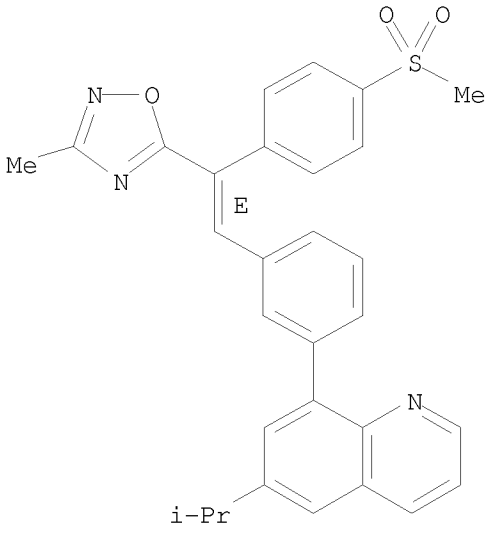
RN 346629-42-3 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



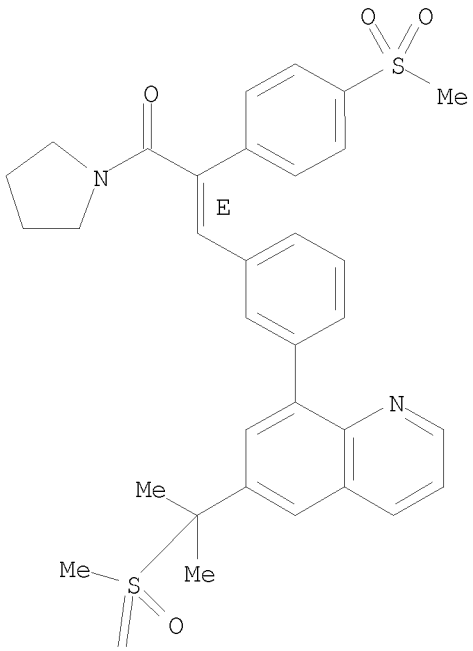
RN 346629-43-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-44-5 CAPLUS
CN 2-Propen-1-one, 3-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-, (2E)- (CA INDEX NAME)

Double bond geometry as shown.



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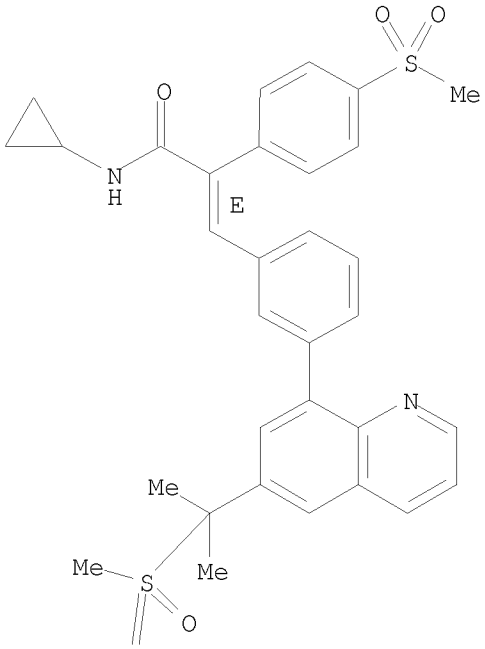
RN 346629-45-6 CAPLUS
CN Benzeneacetamide, N-cyclopropyl-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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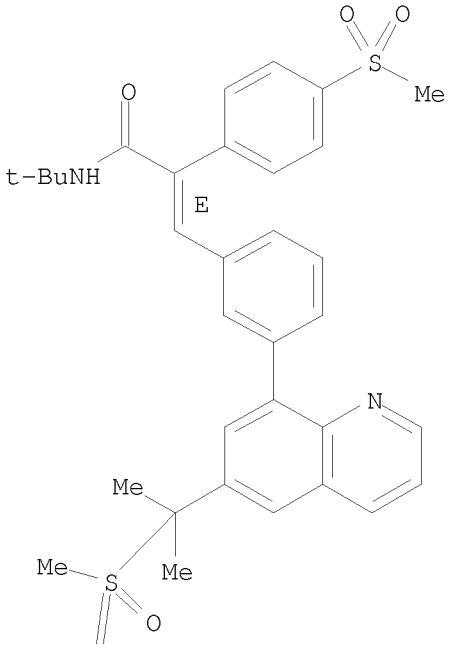
RN 346629-46-7 CAPLUS
CN Benzeneacetamide, N-(1,1-dimethylethyl)-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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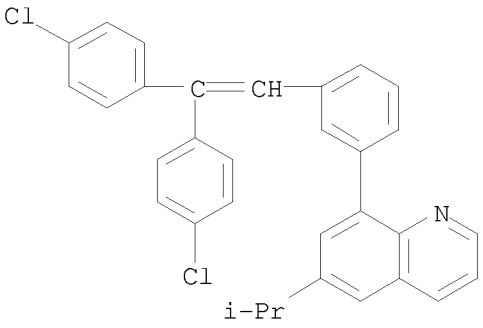
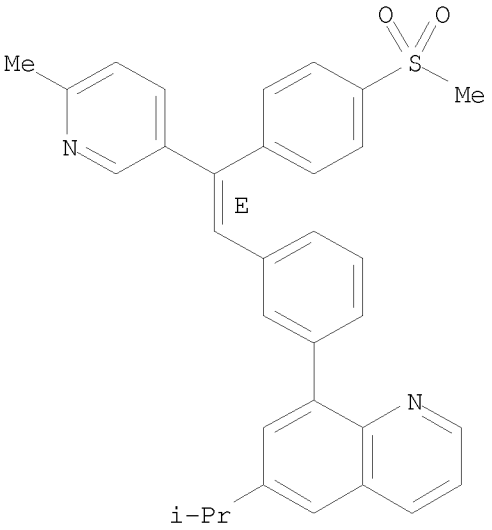
RN 346629-47-8 CAPLUS
CN Quinoline, 8-[3-[2,2-bis(4-chlorophenyl)ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)



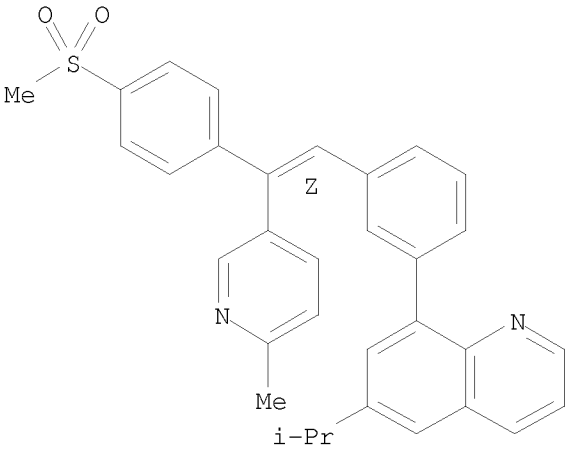
RN 346629-48-9 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



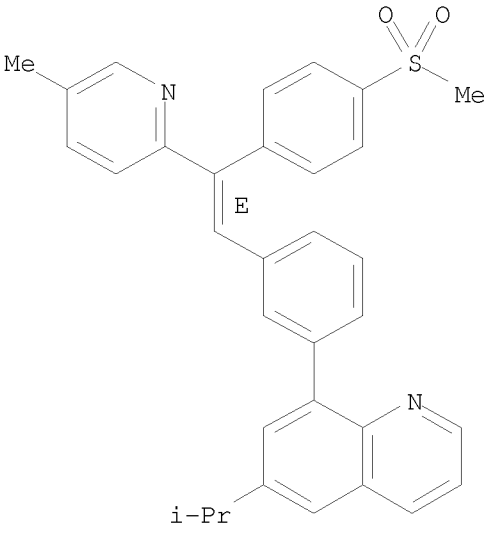
RN 346629-49-0 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1Z)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



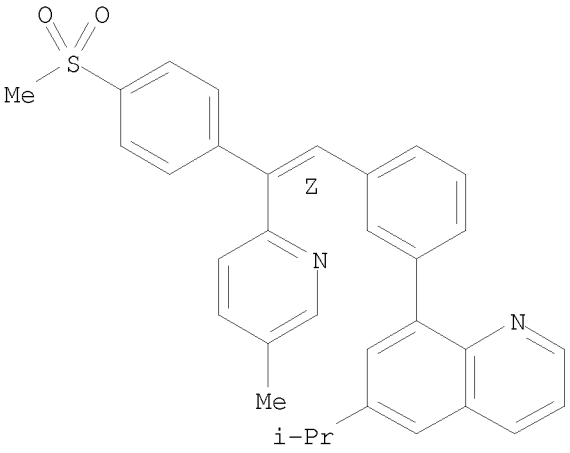
RN 346629-50-3 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

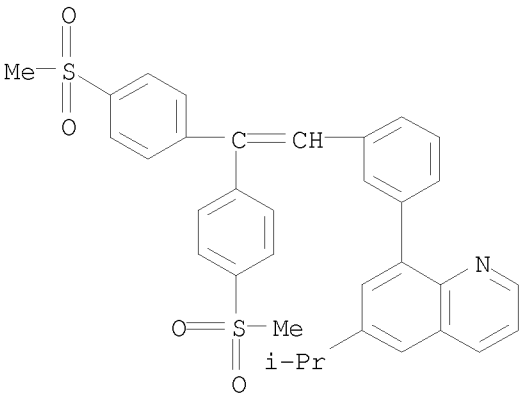


RN 346629-51-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

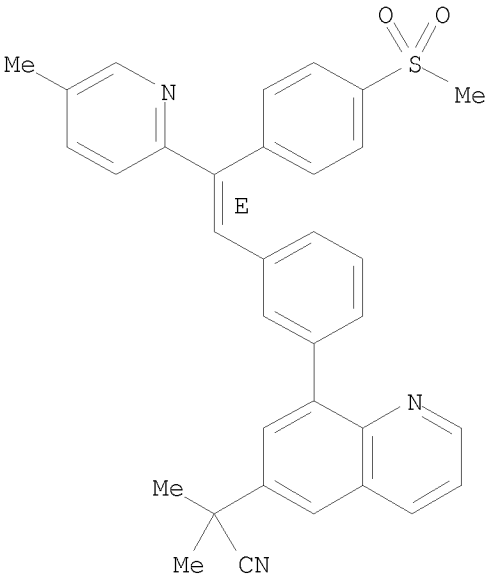


RN 346629-52-5 CAPLUS
CN Quinoline, 8-[3-[2,2-bis[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)



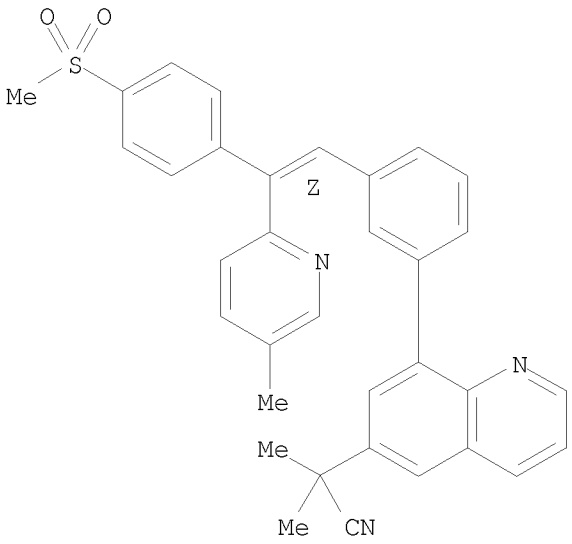
RN 346629-53-6 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-54-7 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-57-0 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

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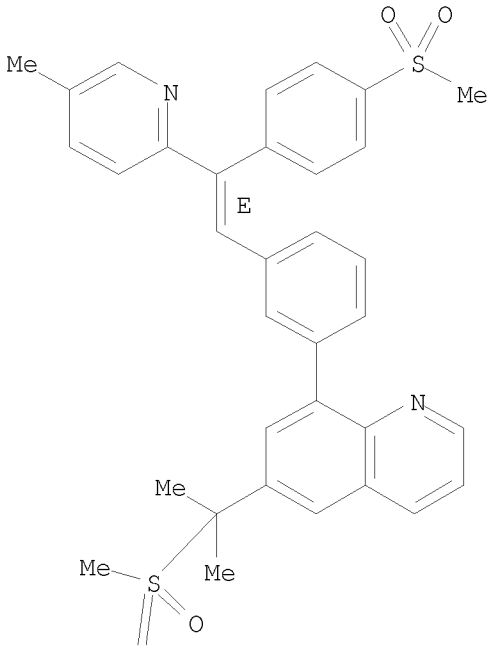

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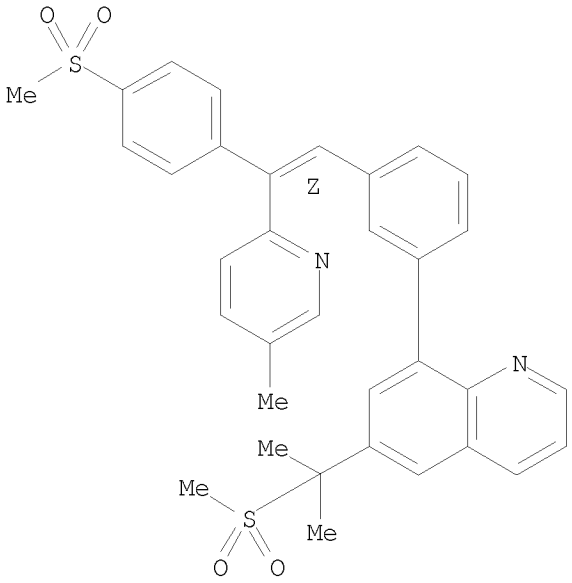
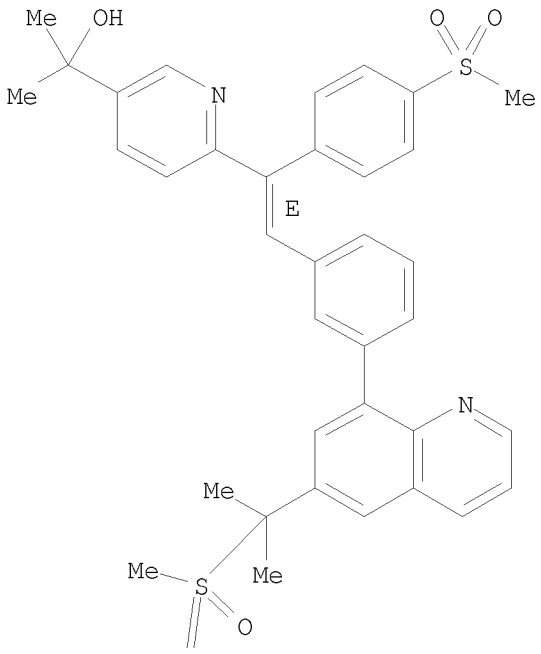
RN 346629-58-1 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-59-2 CAPLUS
CN 3-Pyridinemethanol, α,α-dimethyl-6-[(1E)-2-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.



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O

RN 346630-04-4 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-, sulfate (1:1) (CA INDEX NAME)

CM 1

CRN 346629-30-9
CMF C31 H29 N3 O5 S2

Double bond geometry as shown.

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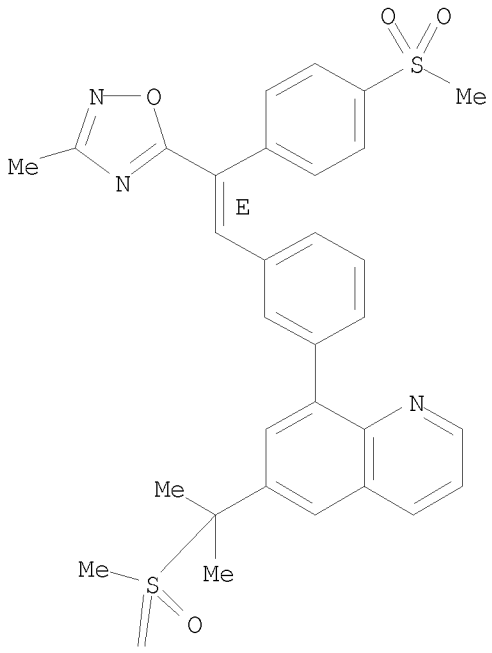

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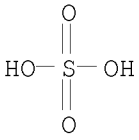
O

CM 2

CRN 7664-93-9
CMF H2 O4 S



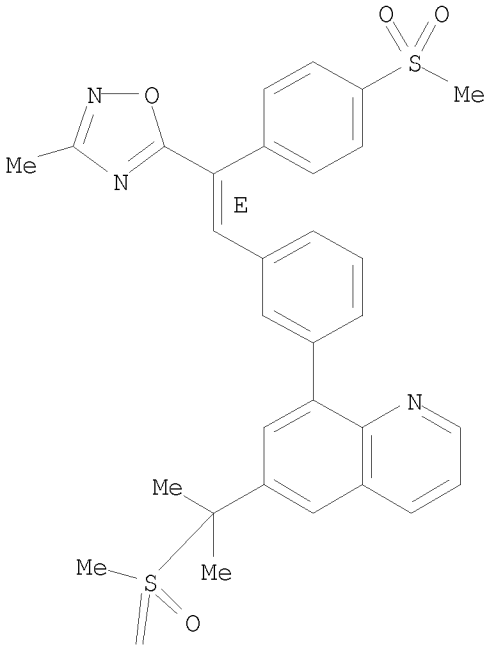
RN 346630-05-5 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 346629-30-9
CMF C31 H29 N3 O5 S2

Double bond geometry as shown.

PAGE 1-A



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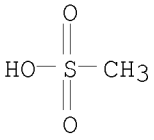
CM 2

CRN 75-75-2
CMF C H4 O3 S



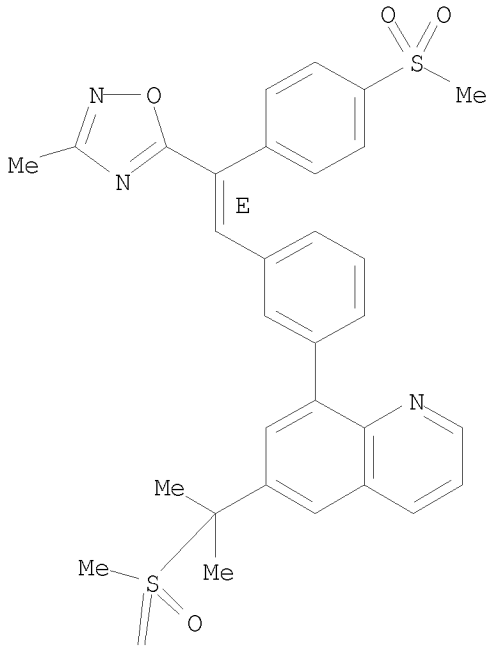
RN 346630-06-6 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-, 4-methylbenzenesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 346629-30-9
CMF C31 H29 N3 O5 S2

Double bond geometry as shown.

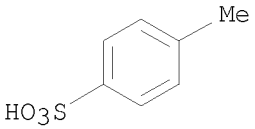
PAGE 1-A



PAGE 2-A

CM 2

CRN 104-15-4
CMF C7 H8 O3 S



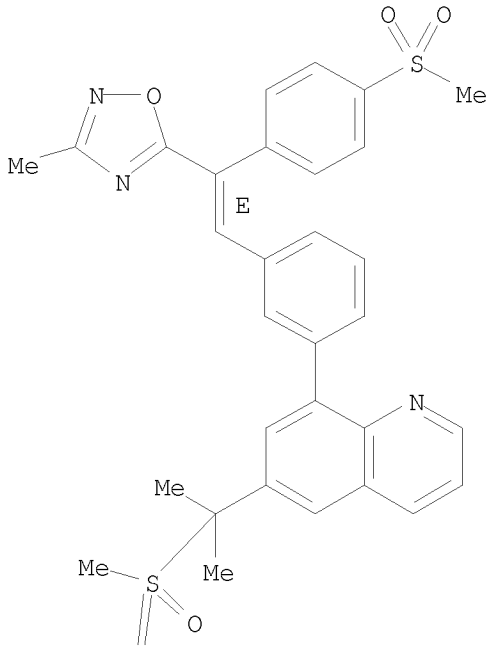
RN 346630-07-7 CAPLUS
CN 2-Naphthalenesulfonic acid, compd. with 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]quinoline (1:1) (CA INDEX NAME)

CM 1

CRN 346629-30-9
CMF C31 H29 N3 O5 S2

Double bond geometry as shown.

PAGE 1-A



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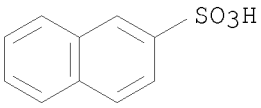
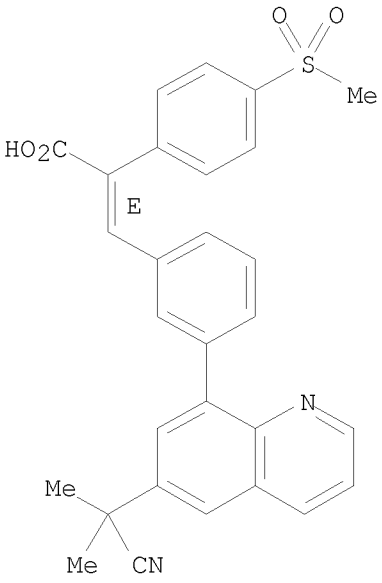
CM 2

CRN 120-18-3
CMF C10 H8 O3 S

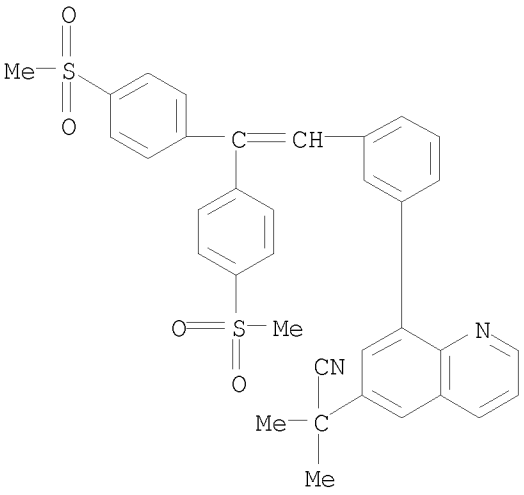


RN 455948-57-9 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

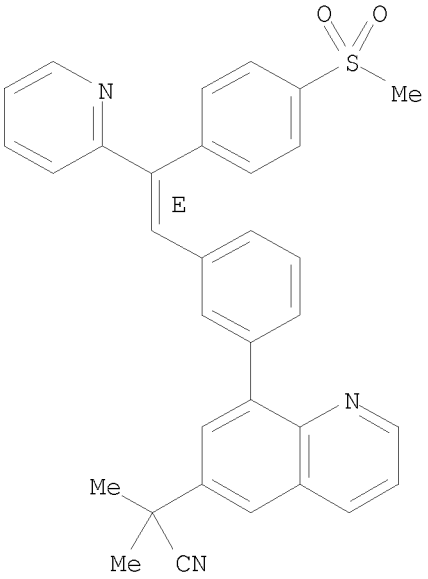


RN 455948-59-1 CAPLUS
CN 6-Quinolineacetonitrile, 8-[3-[2,2-bis[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-α,α-dimethyl- (CA INDEX NAME)



RN 455948-60-4 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridinyl)ethenyl]phenyl]- (CA INDEX NAME)

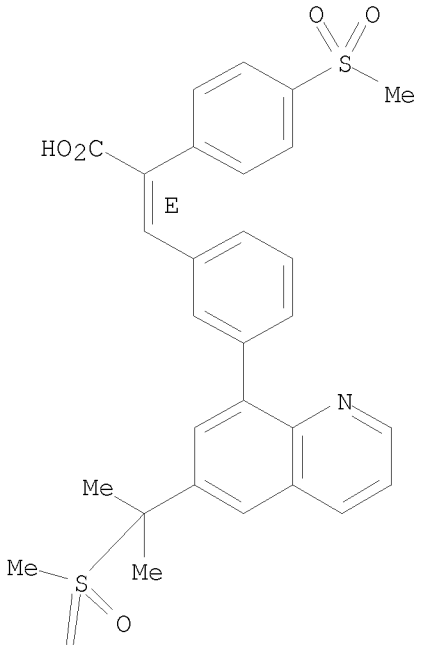
Double bond geometry as shown.



IT 346629-38-7P, (E)-3-[3-[6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of (alkenylaryl)quinoline phosphodiesterase-4 inhibitors with anti-inflammatory and anti-allergic activity)
RN 346629-38-7 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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IT 346630-09-9P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polymorph Form A and Form B, PDE4 inhibitor; preparation of (alkenylaryl)quinoline phosphodiesterase-4 inhibitors with anti-inflammatory and anti-allergic activity)

RN 346630-09-9 CAPLUS

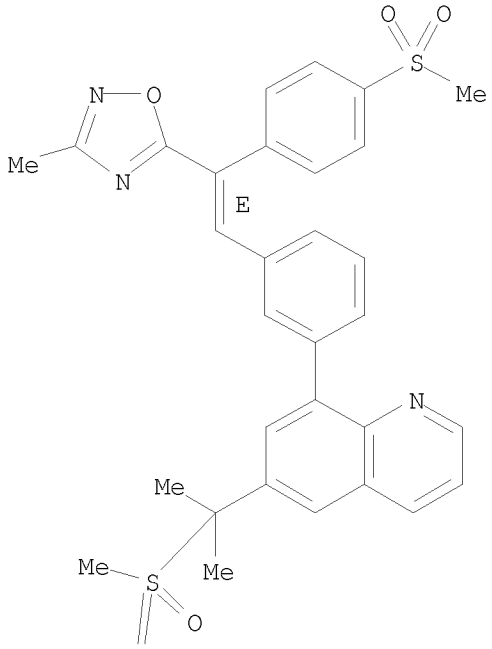
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-, benzenesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 346629-30-9
CMF C31 H29 N3 O5 S2

Double bond geometry as shown.

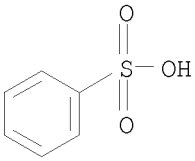
PAGE 1-A



PAGE 2-A

CM 2

CRN 98-11-3
CMF C6 H6 O3 S

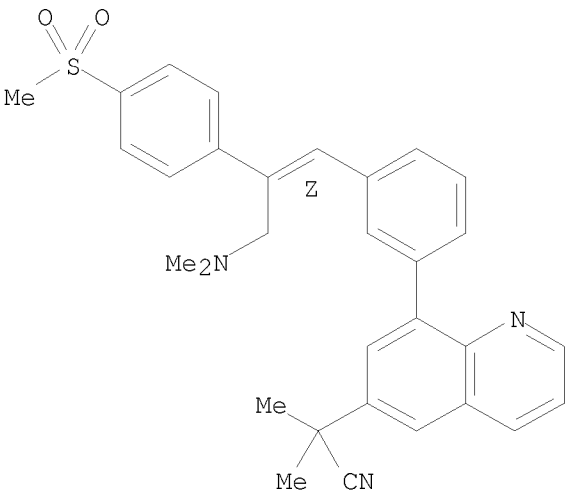


IT 346629-60-5DP, salts
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (alkenylaryl)quinoline phosphodiesterase-4 inhibitors with anti-inflammatory and anti-allergic activity)

RN 346629-60-5 CAPLUS
CN 6-Quinolineacetonitrile, 8-[3-[(1Z)-3-(dimethylamino)-2-[4-(methylsulfonyl)phenyl]-1-propen-1-yl]phenyl]-α,α-dimethyl-

(CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:472677 CAPLUS <<LOGINID::20080618>>
DOCUMENT NUMBER: 135:76803
TITLE: Synthesis and use of substituted 8-arylquinolines (and sulfonic acid salts thereof) as inhibitors of phosphodiesterase-4
INVENTOR(S): Deschenes, Denis; Dube, Daniel; Gallant, Michel; Girard, Yves; Lacombe, Patrick; MacDonald, Dwight; Mastracchio, Anthony; Perrier, Helene
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 263 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001046151	A1	20010628	WO 2000-CA1559	20001220
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BR 2000016651	A	20020910	BR 2000-16651	20001220
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PRIORITY APPLN. INFO.:			US 1999-171522P	P	19991222	
			WO 2000-CA1559	W	20001220	

OTHER SOURCE(S): MARPAT 135:76803
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. of formula I are claimed [wherein; S1-3 = H, OH, halo, (substituted)alkyl/alkoxy, NO2 and CN; R1 = H, OH, halo, CO, (cyclo)alkyl, alkenyl, alkoxy, (hetero)aryl, CN, etc.; R2-3 = H, alkyl, halo, heterocycloalkyl, alkoxy, CO, carbamoyl, COOH, alkyl-S(O)0-2-alkyl; etc.; one of R2 or R3 must be (substituted) aryl/heteroaryl and when both R2 and R3 are aryl/heteroaryl then R2 and R3 may be optionally connected by a S, O or alkyl bridge to form a fused three ring system; A = CH, C-ester or CR4 where R4 = aryl, alkyl, heteroaryl, CN, CO, etc.; R2 or R3 may also be joined to R4 by a bond to form a ring]. Over 40 synthetic examples are given. For instance, 4-(methylsulfonyl)phenylacetic acid was condensed with acetamide oxime to give (3-methyl-1,2,4-oxadiazol-5-yl)[4-(methylsulfonyl)phenyl]methane. This intermediate was condensed with 3-bromobenzaldehyde to give the (E)-bromide. Pd-mediated coupling of the (E)-bromide, via the intermediate pinacol boronate derivative (not isolated), to the substituted 8-bromoquinoline furnished biaryl II. Several sulfonic acid salts of II as well as 2 polymorphs of the benzenesulfonic acid salt of II were characterized (NMR, XRPD, etc.). In an assay of LPS and fMLP-induced TNF-α and LTB4 production in whole blood (surrogate markers for PDE-4 inhibition), example compds. had IC50 = 0.04 to 8.71 μM. Compds. of the invention also inhibited a type-IV cAMP-specific PDE, IC50 = 0.14 to 10.24 nM. A method to treat/prevent asthma, chronic bronchitis, chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis, etc. is a claimed use of the invention.

IT 346629-38-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(and drug candidates; synthesis and use of substituted 8-arylquinolines (and sulfonic acid salts thereof) as inhibitors of phosphodiesterase-4)

RN 346629-38-7 CAPLUS

CN Benzeneacetic acid, α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

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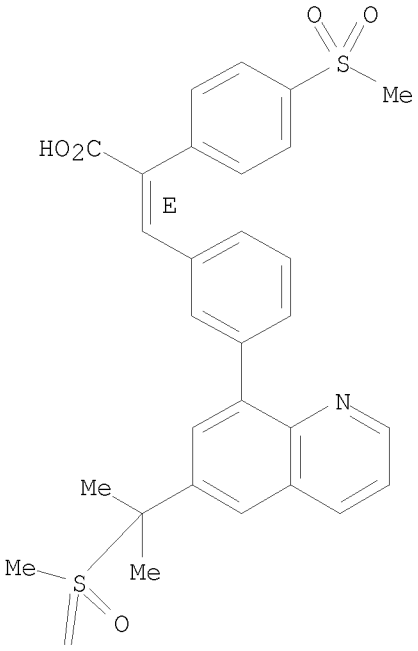

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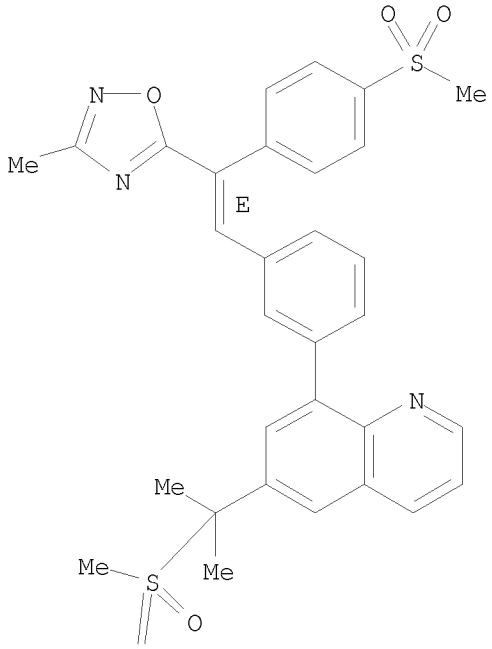
IT 346629-30-9P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(drug candidates; synthesis and use of substituted 8-arylquinolines (and sulfonic acid salts thereof) as inhibitors of phosphodiesterase-4)

RN 346629-30-9 CAPLUS

CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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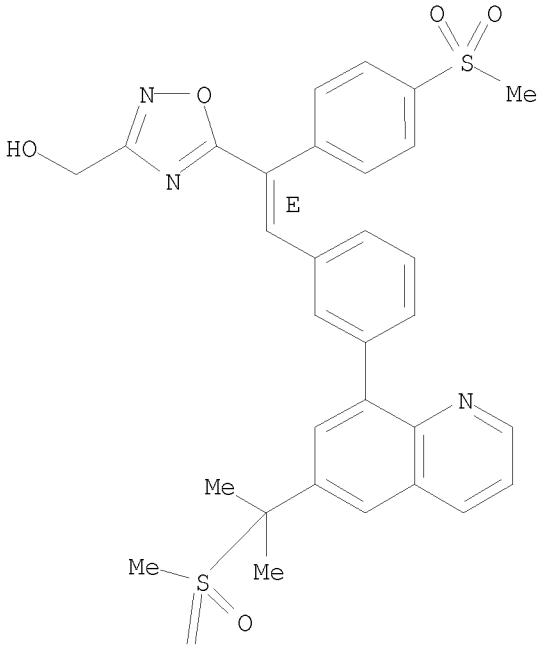
IT 346629-35-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); USES (Uses)
(drug candidates; synthesis and use of substituted 8-arylquinolines (and sulfonic acid salts thereof) as inhibitors of phosphodiesterase-4)
RN 346629-35-4 CAPLUS
CN 1,2,4-Oxadiazole-3-methanol, 5-[(1E)-2-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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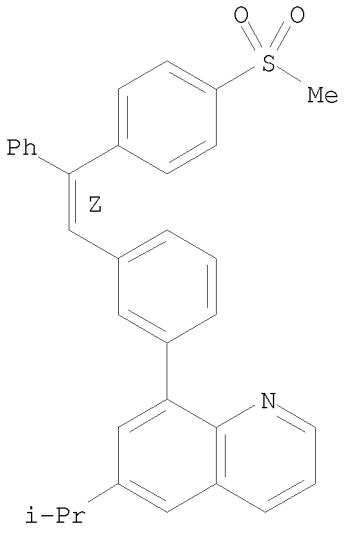
IT 346629-17-2P 346629-18-3P 346629-19-4P
346629-20-7P 346629-21-8P 346629-22-9P
346629-23-0P 346629-24-1P 346629-25-2P
346629-26-3P 346629-27-4P 346629-28-5P
346629-29-6P 346629-31-0P 346629-32-1P
346629-33-2P 346629-34-3P 346629-36-5P
346629-39-8P 346629-40-1P 346629-41-2P
346629-42-3P 346629-43-4P 346629-44-5P
346629-45-6P 346629-46-7P 346629-47-8P
346629-48-9P 346629-49-0P 346629-50-3P
346629-51-4P 346629-52-5P 346629-53-6P
346629-54-7P 346629-55-8P 346629-56-9P
346629-57-0P 346629-58-1P 346629-59-2P
346629-60-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidates; synthesis and use of substituted 8-arylquinolines (and sulfonic acid salts thereof) as inhibitors of phosphodiesterase-4)

RN 346629-17-2 CAPLUS

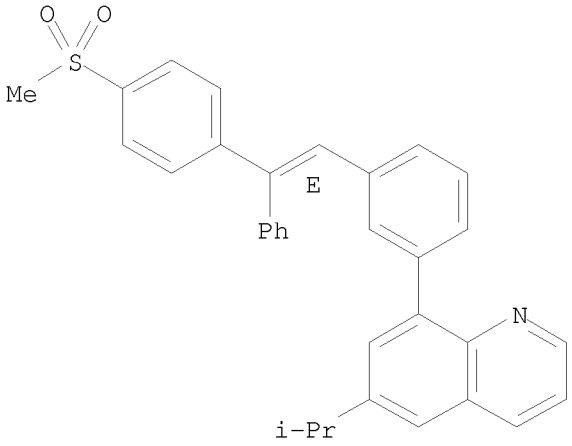
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1Z)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

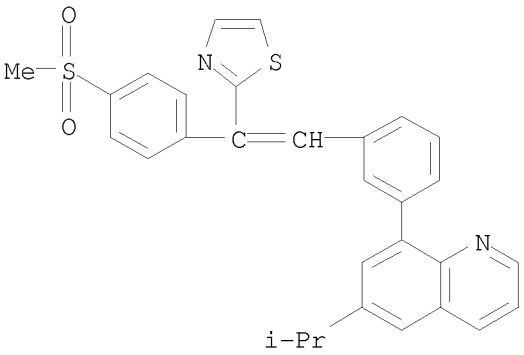


RN 346629-18-3 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

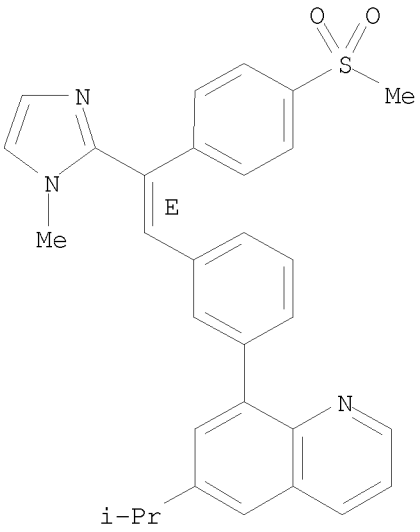


RN 346629-19-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)



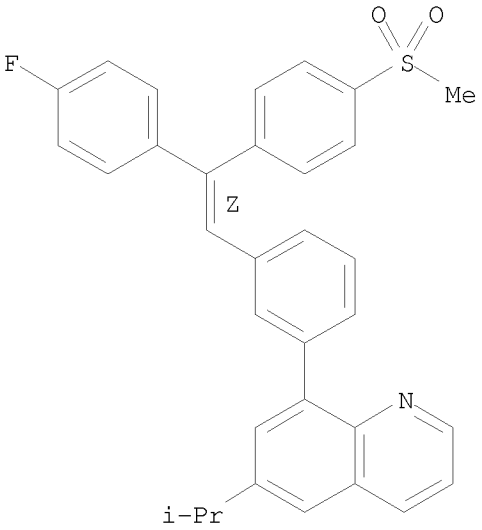
RN 346629-20-7 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



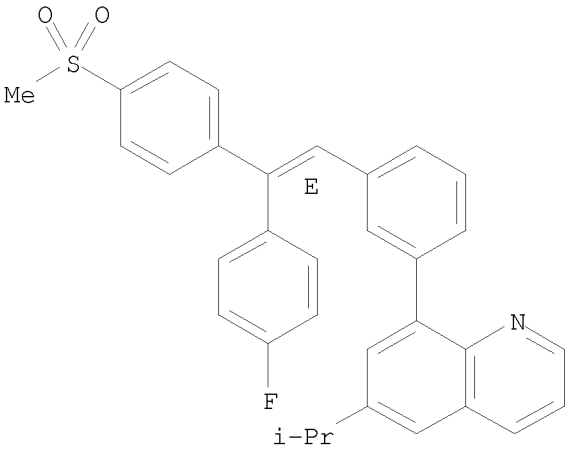
RN 346629-21-8 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)

Double bond geometry as shown.

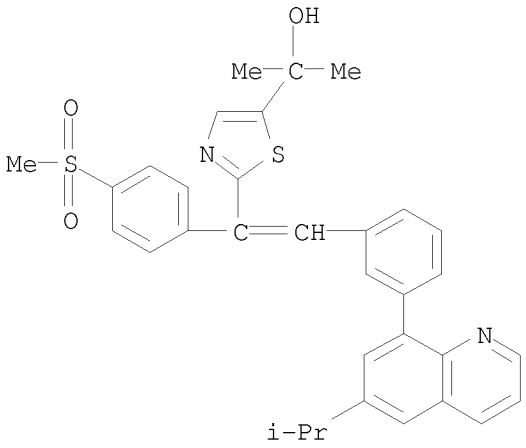


RN 346629-22-9 CAPLUS
CN Quinoline, 8-[3-[(1E)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-(1-methylethyl)- (CA INDEX NAME)

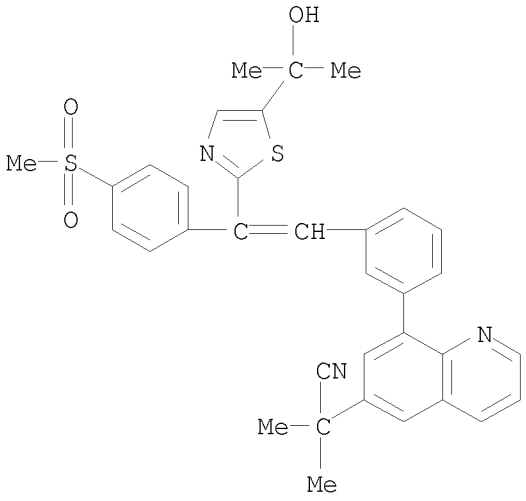
Double bond geometry as shown.



RN 346629-23-0 CAPLUS
CN 5-Thiazolemethanol, α,α-dimethyl-2-[2-[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl]- (CA INDEX NAME)

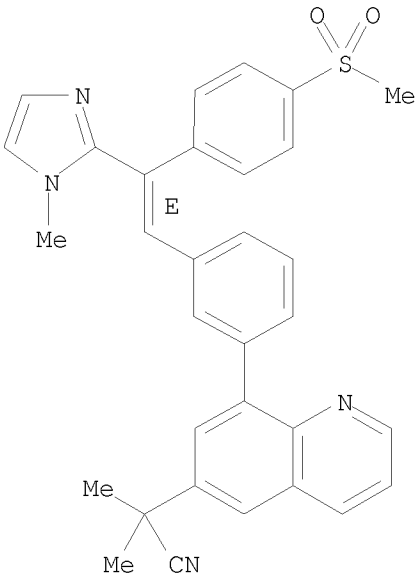


RN 346629-24-1 CAPLUS
CN 6-Quinolineacetonitrile, 8-[3-[2-[5-(1-hydroxy-1-methylethyl)-2-thiazolyl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-α,α-dimethyl- (CA INDEX NAME)



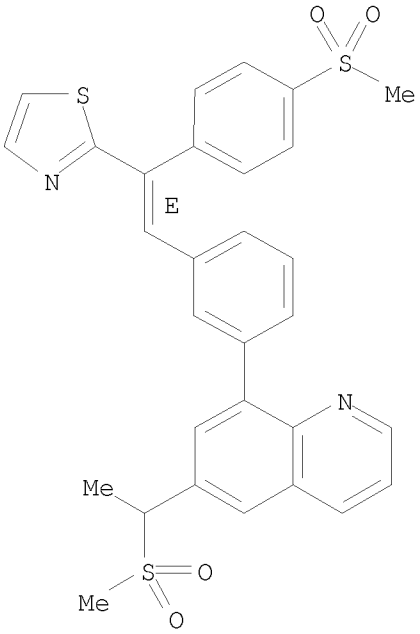
RN 346629-25-2 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-26-3 CAPLUS
CN Quinoline, 6-[1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

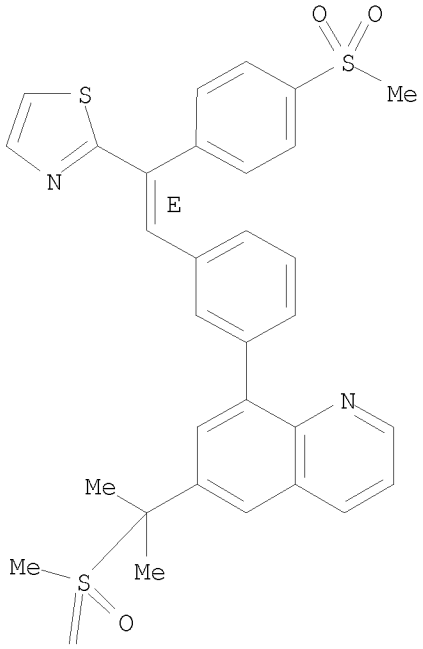
Double bond geometry as shown.



RN 346629-27-4 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1E)-2-[4-(methylsulfonyl)phenyl]-2-(2-thiazolyl)ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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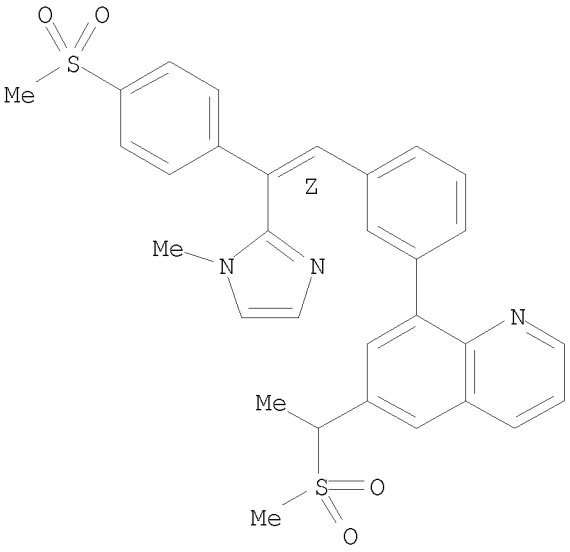
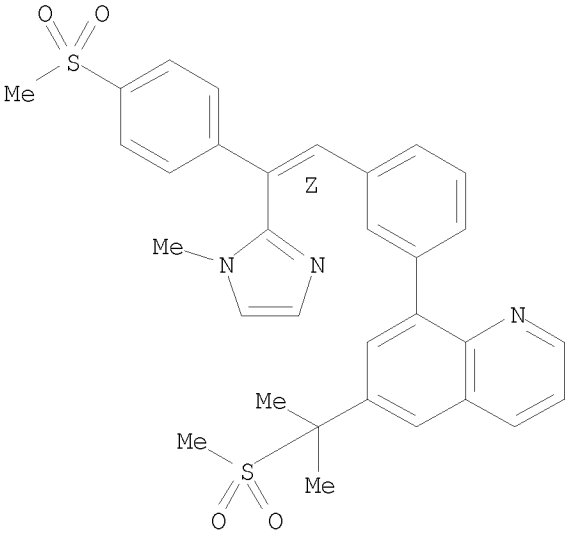
RN 346629-28-5 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.



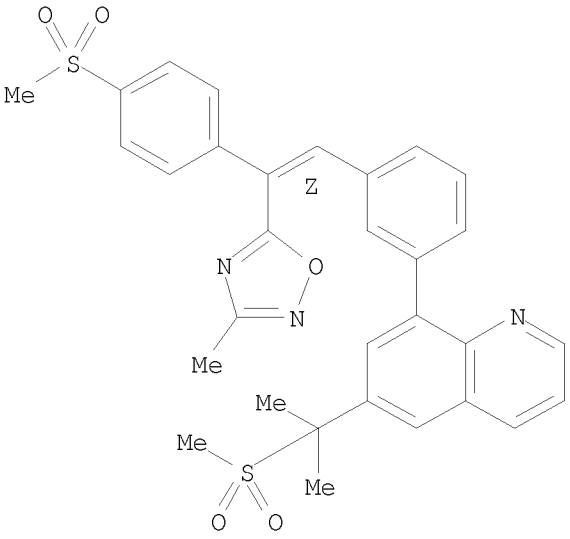
RN 346629-29-6 CAPLUS
CN Quinoline, 8-[3-[(1Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.



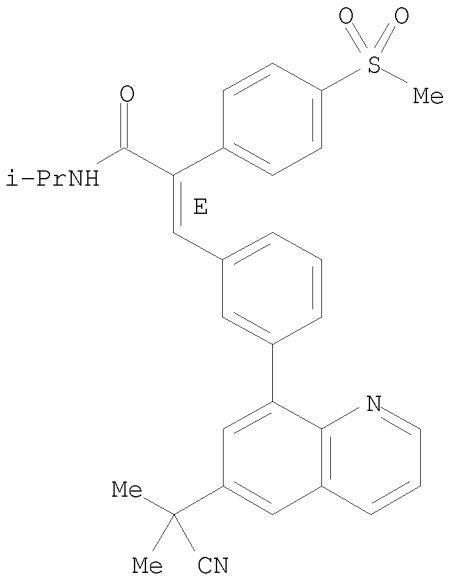
RN 346629-31-0 CAPLUS
CN Quinoline, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-[3-[(1Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



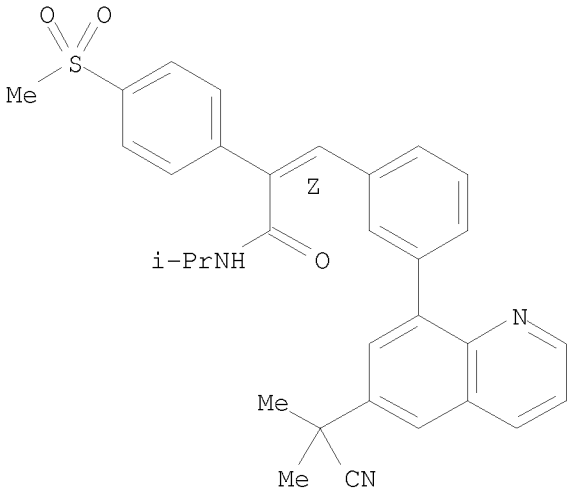
RN 346629-32-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-33-2 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1-methylethyl)-4-(methylsulfonyl)-, (αZ)- (CA INDEX NAME)

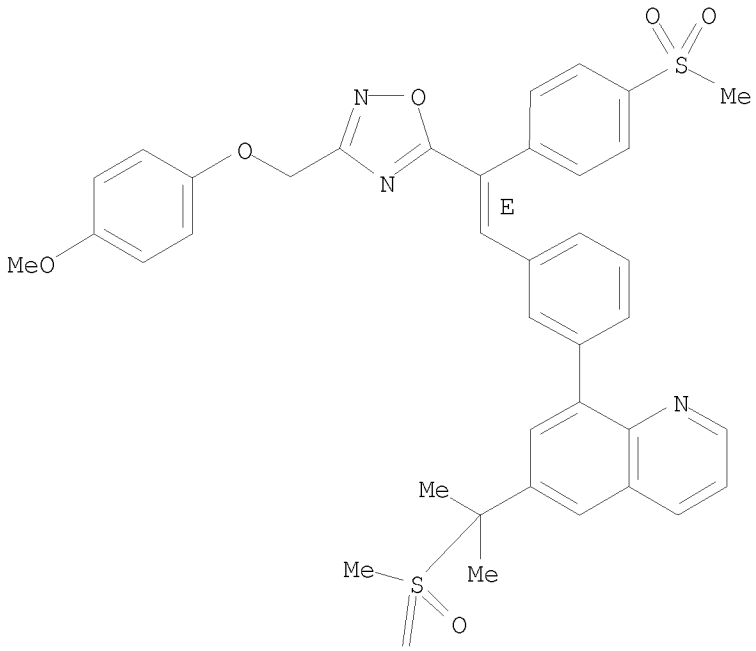
Double bond geometry as shown.



RN 346629-34-3 CAPLUS
CN Quinoline, 8-[3-[(1E)-2-[3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]-6-[1-methyl-1-(methylsulfonyl)ethyl]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

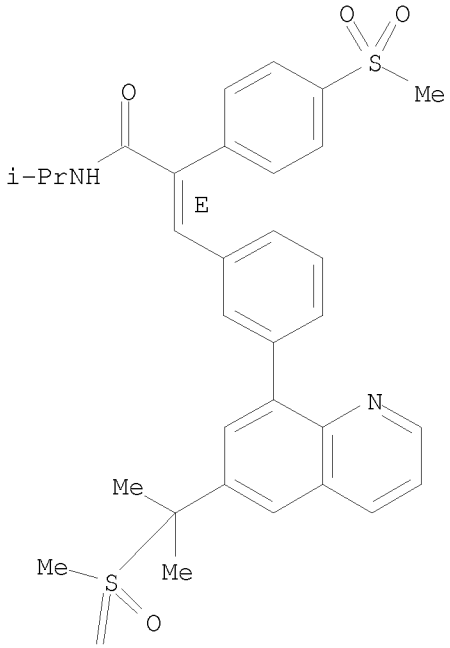


PAGE 2-A

RN 346629-36-5 CAPLUS
CN Benzeneacetamide, N-(1-methylethyl)-α-[[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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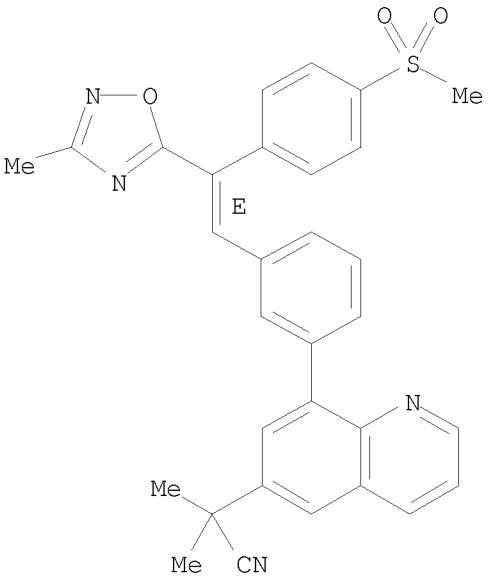
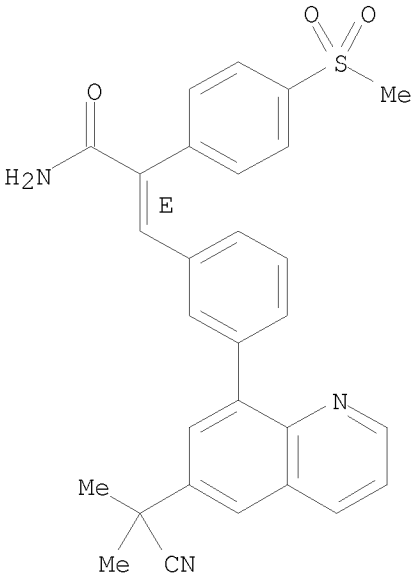
RN 346629-39-8 CAPLUS
CN 6-Quinolineacetonitrile, α,α-dimethyl-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.



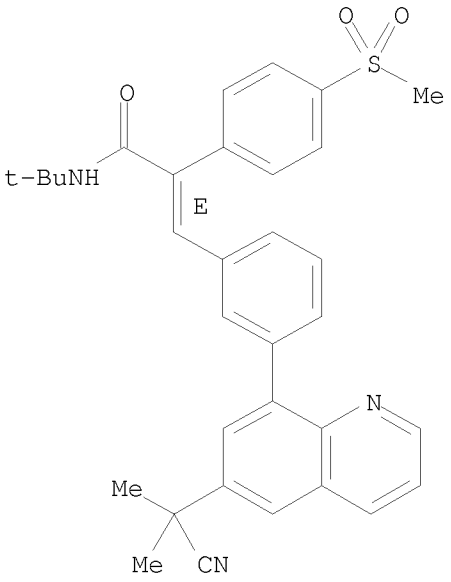
RN 346629-40-1 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



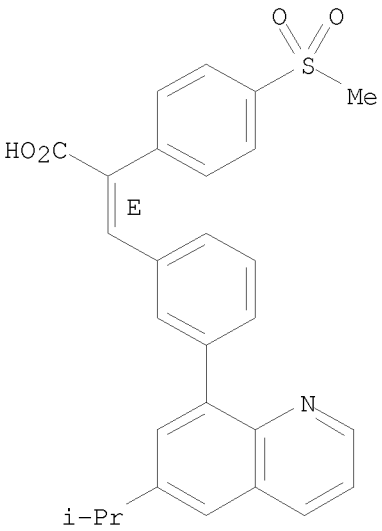
RN 346629-41-2 CAPLUS
CN Benzeneacetamide, α-[[3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl]methylene]-N-(1,1-dimethylethyl)-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



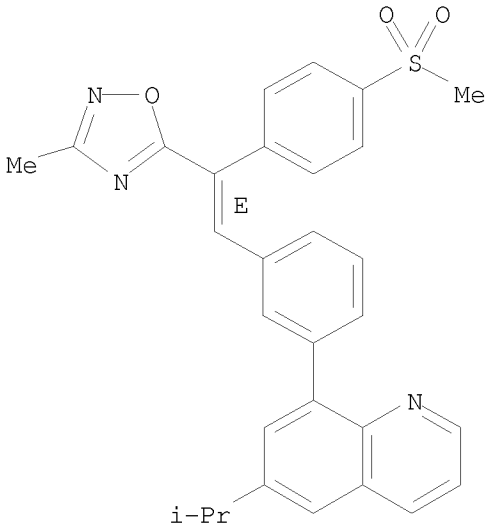
RN 346629-42-3 CAPLUS
CN Benzeneacetic acid, α-[[3-[6-(1-methylethyl)-8-quinolinyl]phenyl]methylene]-4-(methylsulfonyl)-, (αE)- (CA INDEX NAME)

Double bond geometry as shown.



RN 346629-43-4 CAPLUS
CN Quinoline, 6-(1-methylethyl)-8-[3-[(1E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl]- (CA INDEX NAME)

Double bond geometry as shown.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